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Transformasi Pendekatan Blok Saraf Sensoris sebagai Strategi Prosedur Bebas Nyeri

Physiologically Based Pharmacokinetic (PBPK) Simulation of Supratherapeutic Meropenem Exposure and Potential Pharmacokinetics/Pharmacodynamics (PK/PD) Discordance in a Critically Ill

Pediatric Patient: A Case Report

hal. 38

Multi-Scale Mechanisms of *Phaleria macrocarpa* in Liver Fibrosis: From Hepatic Stellate Cell Reprogramming to Systems Pharmacology Insights

hal. 50

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Transformasi Blok Saraf Sensoris untuk Prosedur Bebas Nyeri dengan *Levobupivacaine*

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Abstrak

Nyeri prosedural merupakan konsekuensi biologis dari aktivasi nosiseptor perifer, transmisi impuls melalui serabut saraf sensoris, pemrosesan spinal, dan integrasi kortikal yang akhirnya menghasilkan pengalaman nyeri sebagai peristiwa tubuh sekaligus kesadaran. Dalam praktik klinis modern, strategi bebas nyeri tidak lagi cukup dipahami sebagai pemberian analgesik setelah nyeri terjadi, melainkan sebagai intervensi presisi pada jalur penghantaran nyeri sebelum impuls nosiseptif berkembang menjadi respons sistemik dan beban psikologis. Blok saraf sensoris menjadi pendekatan klinis yang penting karena bekerja langsung pada struktur transmisi perifer, dengan tujuan menghambat konduksi impuls nyeri tanpa harus menimbulkan depresi kesadaran yang luas. *Levobupivacaine*, suatu anestetik lokal golongan amino-amida dengan profil kerja panjang dan stereoselektivitas yang lebih menguntungkan dibandingkan rasemat *bupivacaine*, menawarkan dasar farmakologis yang relevan bagi transformasi ini. Dengan menghambat *voltage-gated sodium channel* pada membran saraf, *levobupivacaine* menstabilkan keadaan inaktif kanal, menurunkan eksitabilitas neuron, dan memutus rangkaian transmisi sensoris secara reversibel. Perspektif medis ini menempatkan blok saraf sensoris bukan sekadar sebagai teknik anestesi regional, melainkan bagian dari pergeseran klinis menuju prosedur yang lebih terarah, berbasis mekanisme, tepat secara anatomi, berpusat pada pasien, lebih manusiawi, dan lebih selaras dengan fisiologi nyeri. Tantangan dari pendekatan ini yaitu terletak pada pemilihan pasien, pemahaman anatomi, akurasi teknik, pemantauan toksisitas, serta integrasi blok sensoris ke dalam tata laksana perioperatif yang rasional.

Kata kunci: blok saraf sensoris, *levobupivacaine*, nyeri prosedural, anestesi regional, analgesia perioperatif

Abstract

Procedural pain is a biological consequence arises from the activation of peripheral nociceptors, the transmission of impulse through sensory nerve fibers, spinal processing, and cortical integration that transforms tissue injury into a conscious pain experience. Modern clinical practice increasingly recognizes that pain-free procedures should not be limited to postprocedural analgesia, but should involve precise interventions targeting pain transmission pathways before nociceptive impulses evolve into a systemic responses and psychological burden. Sensory nerve block represents an important clinical approach because it acts directly on peripheral transmission structures, aiming to inhibit pain impulse conduction without inducing extensive depression of consciousness. Levobupivacaine, a long-acting amino-amide local anesthetic and the S-enantiomer of bupivacaine, provides a pharmacologically relevant option for this transformation. By inhibiting voltage-gated sodium channels on neuronal membranes and stabilizing their inactive state, levobupivacaine reduces neuronal excitability and reversibly interrupts the sensory transmission pathway. This medical perspective frames sensory nerve block not merely as a regional anesthetic technique, but as part of a broader shift toward procedures that are more targeted, mechanism-based, anatomically precise, patient-centered care, more humane, and align with the physiology of pain. The challenges associated with this approach include appropriate patient selection, comprehensive

anatomical understanding, technical precision, toxicity awareness, and the integration of sensory nerve blocks into rational perioperative pain management.

Keywords: sensory nerve block, levobupivacaine, procedural pain, regional anesthesia, perioperative analgesia

Pendahuluan

Nyeri prosedural bermula jauh sebelum pasien menyebut kata “sakit”. Nyeri pada tingkat jaringan, tindakan insisi, tusukan jarum, manipulasi mekanik, peregang kapsul, iritasi kimia, atau inflamasi lokal akan mengubah lingkungan mikro di sekitar ujung saraf bebas. Sel yang cedera akan melepaskan mediator seperti prostaglandin, bradikinin, serotonin, *histamine*, ion hidrogen, *adenosine triphosphate*, dan berbagai sitokin yang menurunkan ambang aktivasi nosiseptor.^{1,2} Ujung saraf yang semula tenang menjadi lebih mudah tereksitasi, kanal ion pada membran neuron terbuka, gradien listrik berubah, dan impuls mulai berjalan dari perifer menuju medula spinalis.² Di titik inilah, nyeri sebagai pengalaman manusiawi yang tampak sederhana, sebenarnya lahir dari rangkaian biologi yang sangat teratur.

Selama bertahun-tahun, banyak prosedur medis dipahami dengan logika yang relatif linier, di mana tindakan dilakukan, muncul nyeri, kemudian obat analgesik diberikan. Pendekatan ini memang memiliki tempat, terutama dalam tata laksana nyeri pascaproedur. Namun semakin dalam pemahaman terhadap fisiologi nyeri, semakin jelas bahwa nyeri bukan sekadar gejala yang datang setelah terjadinya kerusakan jaringan. Nyeri merupakan suatu proses transmisi, amplifikasi, modulasi, dan ingatan biologis. Sekali impuls nosiseptif masuk ke sistem saraf pusat secara kuat dan berulang, respons tubuh tidak hanya berupa rasa tidak nyaman, melainkan juga aktivasi simpatis, peningkatan denyut jantung, perubahan tekanan darah, pelepasan hormon stres, ketegangan otot, gangguan tidur, kecemasan, dan pada sebagian keadaan, sensitisasi sentral yang membuat nyeri menjadi lebih mudah menetap.³

Oleh karena itu, transformasi penting dalam praktik prosedural modern terletak pada pergeseran paradigma dari sekadar “mengobati nyeri” menuju “mencegah transmisi nyeri secara tepat”. Pergeseran ini tampak sederhana namun memiliki makna yang besar. Fokus klinis bergeser dari pusat kesadaran menuju jalur perifer, dari sedasi yang luas menuju blok yang terarah, dari respons setelah kejadian menuju intervensi sebelum impuls mencapai sistem saraf pusat. Blok saraf sensoris berdiri tepat di tengah perubahan ini. Prosedur ini tidak melumpuhkan seluruh tubuh, tidak selalu menghilangkan kesadaran, dan tidak membebani sistem respirasi atau kardiovaskular sebagaimana dapat terjadi pada anestesi umum, melainkan bekerja pada kabel biologis yang membawa pesan nyeri. Dengan memutus penghantaran impuls secara sementara, prosedur dapat berlangsung dengan beban nosiseptif yang jauh lebih terkendali.⁴

Saraf perifer di tubuh manusia bukanlah sebuah struktur yang homogen. Satu berkas saraf mengandung serabut motorik, sensoris, otonom, dan nosiseptif, di mana masing-masing memiliki diameter, tingkat mielinisasi, serta kecepatan konduksi yang berbeda. Serabut A-delta yang bermielin tipis bertugas untuk menghantarkan impuls nyeri tajam dan cepat, sedangkan serabut C yang tidak bermielin bertugas untuk menghantarkan impuls nyeri tumpul, terbakar, lambat, dan lebih menyebar.² Serabut A-beta bertugas untuk menghantarkan sensasi raba dan tekanan, sementara serabut motorik mengatur kontraksi otot. Perbedaan biologis ini menjelaskan mengapa blok saraf dapat menghasilkan urutan efek yang tidak selalu seragam: rasa nyeri menghilang, sensasi raba berubah, suhu tidak lagi dikenali dengan jelas, sementara kekuatan motorik dapat berkurang tergantung konsentrasi obat, lokasi injeksi, volume, dan kedekatan obat dengan *fascicle* tertentu. Tujuan klinis blok saraf sensoris adalah mengendalikan transmisi nyeri dengan gangguan motorik seminimal mungkin, sejauh dimungkinkan oleh konteks prosedur.

Levobupivacaine menjadi agen farmakologis yang relevan dalam lanskap ini karena molekul tersebut membawa karakteristik anestetik lokal kerja panjang dengan profil yang sesuai untuk analgesia regional. Secara kimia, *levobupivacaine* adalah enansiomer S dari *bupivacaine*, yang termasuk golongan amino-amida, bersifat lipofilik, berikatan cukup kuat

dengan protein plasma, dan memiliki durasi kerja yang panjang.⁵ Pada membran neuron, obat ini menghambat *voltage-gated sodium channel*, terutama ketika kanal berada dalam keadaan terbuka atau inaktif selama depolarisasi berulang.⁶ Akibatnya, influks natrium ke dalam neuron berkurang, kenaikan potensial aksi terhambat, dan impuls tidak dapat menyalur secara efektif di sepanjang akson. Nyeri tidak “dihapus” dari kesadaran secara abstrak, namun pesan biologisnya berhenti di jalur penghantaran.

Poin penting dari pendekatan ini adalah bahwa kerja *levobupivacaine* tidak dapat dipahami hanya sebagai efek farmakologis tunggal, melainkan bergantung pada anatomi ruang tempat obat disuntikkan, difusi melalui jaringan ikat, pH lokal, derajat inflamasi, kepadatan vaskular, ukuran saraf, serta teknik klinis yang digunakan. Pada jaringan yang mengalami inflamasi, pH yang lebih rendah dapat meningkatkan jumlah fraksi obat yang terionisasi, sehingga penetrasi ke membran saraf dapat berubah.⁴ Pada area dengan kepadatan vaskular yang tinggi, absorpsi sistemik lebih cepat terjadi, durasi efek lokal dapat berkurang, sehingga risiko paparan sistemik perlu diperhatikan. Pada blok pleksus atau blok saraf perifer besar, volume dan konsentrasi menentukan seberapa luas obat menyebar dan seberapa dalam blok terjadi. Dengan kata lain, keberhasilan blok sensoris tidak hanya ditentukan oleh pilihan molekul, tetapi oleh perjumpaan antara molekul, jaringan, anatomi, dan keterampilan klinis.

Di sinilah transformasi pendekatan menjadi tampak lebih nyata. Blok saraf sensoris yang baik bukanlah tindakan injeksi yang dilakukan secara kasar berdasarkan perkiraan lokasi nyeri. Pendekatan ini menuntut pemetaan anatomi, pemahaman cabang saraf, orientasi terhadap lapisan fascia, serta kesadaran terhadap struktur vaskular dan organ sekitar. Perkembangan panduan ultrasonografi memperhalus paradigma ini. Dengan visualisasi *real-time*, klinisi dapat melihat saraf, jarum, penyebaran anestesi lokal, pembuluh darah, otot, tendon, dan bidang fascia.⁷ Obat tidak lagi “dikirimkan” ke area umum, melainkan ditempatkan sedekat mungkin pada kompartemen yang relevan. Presisi anatomis ini mengurangi kebutuhan volume obat yang berlebihan, memperbaiki kualitas blok, serta memberi ruang lebih besar bagi strategi analgesia yang hemat obat namun tetap efektif.^{7,8}

Dalam prosedur sederhana hingga sedang, blok saraf sensoris dapat mengubah pengalaman pasien secara signifikan. Pasien yang tetap sadar tetapi tidak merasakan nyeri, berada dalam kondisi psikologis yang berbeda dibandingkan pasien yang memulai prosedur dengan kecemasan terhadap timbulnya rasa sakit. Tubuh tidak mengalami lonjakan simpatis yang sama kuat, otot tidak selalu menegang sebagai respons protektif, pernapasan dapat tetap spontan, dan komunikasi antara dokter dengan pasien dapat berlangsung bila diperlukan. Pada pasien tertentu, terutama mereka yang memiliki risiko respirasi, usia lanjut, komorbiditas kardiovaskular, atau kebutuhan pemulihan cepat, pendekatan ini membuka kemungkinan klinis yang lebih lembut. Tidak semua prosedur harus dibawa ke kedalaman anestesi yang sama dan tidak semua nyeri memerlukan pembungkaman kesadaran.

Walaupun demikian, pendekatan bebas nyeri tidak boleh dimaknai sebagai penyederhanaan risiko. Anestesi lokal tetap memiliki potensi toksisitas sistemik bila masuk ke dalam sirkulasi dengan kadar yang bermakna, baik melalui injeksi intravaskular secara tidak sengaja maupun absorpsi yang berlebihan. Gejala dapat bermula dari sensasi rasa logam di mulut, tinitus, parestesia perioral, pusing, gelisah, tremor, hingga kejang. Pada kadar yang lebih tinggi, sistem kardiovaskular dapat terdampak melalui gangguan konduksi, penurunan kontraktilitas, aritmia, hipotensi, bahkan kolaps sirkulasi. *Levobupivacaine* dikembangkan dan digunakan dengan perhatian terhadap profil stereoselektif yang cenderung lebih menguntungkan dibandingkan rasemat *bupivacaine*, terutama dalam aspek toksisitas kardiovaskular dan neurologis, tetapi kehati-hatian tetap menjadi syarat klinis.^{5,9} Tidak ada molekul yang membebaskan praktik medis dari disiplin dosis, aspirasi, injeksi bertahap, pemantauan, kesiapan resusitasi, serta ketersediaan terapi emulsi lipid bila terjadi toksisitas anestesi lokal sistemik.¹⁰

Dalam praktik perioperatif, *levobupivacaine* memiliki keunggulan yang paling menonjol bila ditempatkan sebagai bagian dari analgesia multimodal. Blok sensoris dapat mengurangi kebutuhan opioid, menurunkan mual muntah pascaoperasi, mempercepat mobilisasi, serta memperbaiki kenyamanan pasien, namun penggunaannya tidak harus berdiri sendiri.¹¹ Analgesik nonopioid, antiinflamasi, *paracetamol*, teknik infiltrasi lokal, edukasi pasien, pengendalian kecemasan, dan rehabilitasi dini tetap memiliki tempat. Pendekatan yang matang tidak menjadikan satu obat sebagai pusat narasi, melainkan menyusun lapisan-lapisan intervensi yang sesuai dengan fisiologi nyeri.¹² Bila nyeri inflamasi mendominasi, komponen antiinflamasi perlu dipertimbangkan, sebaliknya bila nyeri neuropati menjadi risiko, strategi pemantauan dan intervensi lanjutan diperlukan, dan bila nyeri mekanik muncul akibat mobilisasi, tata laksana tidak cukup hanya dengan blok saraf saat dilakukannya prosedur.

Levobupivacaine juga memberi ruang penting dalam konsep analgesia yang lebih panjang tanpa harus memperpanjang paparan sedatif. Durasi kerja yang panjang memungkinkan pengendalian nyeri melewati fase awal pascatindakan, yaitu fase ketika produksi mediator inflamasi meningkat, jaringan mulai membengkak, dan sistem saraf perifer sangat mudah teriritasi.^{13,14} Fase ini merupakan fase di mana pasien sering mengalami puncak ketidaknyamanan. Bila jalur sensoris telah diblok secara adekuat, tubuh memiliki waktu untuk melewati fase awal cedera dengan beban nosiseptif yang lebih rendah akibat adanya semacam jeda biologis yang diberikan kepada sistem saraf. Jeda ini bukan sekadar memberikan kenyamanan, tetapi dapat membantu mengurangi stres, ketegangan, dan respons nyeri berulang.

Meskipun demikian, durasi panjang juga menuntut edukasi yang memadai. Pasien yang mengalami baal atau penurunan sensasi pada area tertentu perlu memahami bahwa bagian tubuh tersebut harus dilindungi dari trauma, tekanan, panas, atau gerakan berlebihan.¹⁰ Bila blok mengenai saraf yang berdekatan dengan komponen motorik, kelemahan sementara dapat meningkatkan risiko jatuh atau cedera, maka prosedur bebas nyeri bukan hanya menyangkut keberhasilan saat tindakan berlangsung, tetapi juga tata kelola setelah pasien meninggalkan ruang prosedur. Instruksi pascatindakan, pendampingan, evaluasi sensoris-motorik, dan kewaspadaan terhadap gejala yang tidak lazim menjadi bagian dari keseluruhan desain klinis.

Pada tingkatan yang lebih luas, blok saraf sensoris mengubah cara klinisi memandang nyeri. Nyeri bukanlah musuh yang sekadar perlu dihilangkan, melainkan suatu sinyal biologis yang harus dibaca berdasarkan jalurnya. Ada nyeri yang perlu dicegah karena hanya menambah beban prosedural tanpa memberikan manfaat protektif, ada pula nyeri yang perlu dipantau karena dapat menunjukkan komplikasi, iskemia, perdarahan, infeksi, atau cedera jaringan yang berkembang. Oleh karena itu, blok sensoris harus ditempatkan secara cerdas, tidak mengaburkan kemungkinan diagnosis penting, serta tidak menghilangkan kewaspadaan klinis. Pada prosedur tertentu, penghilangan nyeri yang terlalu luas tanpa pemantauan yang memadai dapat menyembunyikan perubahan yang justru perlu diketahui. Presisi bukan hanya berarti tepat sasaran, tetapi juga tepat batas.

Keindahan klinis dari pendekatan ini justru terletak pada keseimbangannya. Di satu sisi, pendekatan ini berani mengintervensi fisiologi nyeri secara langsung dan terarah, dan di sisi lain menolak gagasan bahwa semakin dalam anestesi, selalu berarti semakin baik. Dengan *levobupivacaine*, blok sensoris dapat dirancang untuk memberi durasi analgesia yang memadai, stabilitas tindakan, dan kenyamanan pascatindakan, sambil tetap menghormati variasi anatomi, kerentanan pasien, serta konteks prosedur. Molekul bekerja di tingkat kanal natrium, tetapi keputusan klinis bekerja di tingkat manusia utuh. Di antara keduanya terdapat ruang yang harus diisi oleh pengetahuan, ketelitian, dan kepekaan.

Transformasi menuju prosedur bebas nyeri bukan sebatas transformasi alat, melainkan transformasi cara berpikir. Tubuh pasien tidak lagi dipandang hanya sebagai tempat tindakan dilakukan, melainkan sebagai sistem saraf hidup yang merespons, mengingat, dan menyesuaikan diri. Setiap tusukan, tarikan, tekanan, dan iritasi memiliki konsekuensi

neurofisiologis, dan setiap strategi analgesia memberi pesan balik kepada sistem tersebut. Blok saraf sensoris dengan *levobupivacaine* menawarkan satu cara untuk membuat tindakan medis lebih selaras dengan bahasa tubuh sendiri: menghambat nyeri di jalurnya, mengurangi beban sistemik, dan memberi ruang bagi pemulihan yang lebih tenang. Barangkali di masa depan, ukuran keberhasilan prosedur tidak hanya dinilai dari selesainya tindakan secara teknis, tetapi juga dari seberapa sedikit tubuh harus berteriak untuk melewatinya.

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Transformasi Pendekatan Blok Saraf Sensoris sebagai Strategi Prosedur Bebas Nyeri

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Abstrak

Nyeri selama prosedur medis masih menjadi tantangan utama dalam praktik klinis, terutama pada tindakan bedah minor dan prosedur invasif sederhana. Teknik infiltrasi anestesi lokal konvensional sering kali menyebabkan nyeri tambahan, distorsi jaringan, serta distribusi anestesi yang kurang optimal. Oleh karena itu, diperlukan pendekatan yang lebih sederhana, efektif, dan nyaman bagi pasien. Pendekatan menggunakan blok saraf sensoris menargetkan cabang saraf sensoris perifer sebagai perpanjangan dari sistem saraf pusat yang terletak di area distal. Dengan pemilihan titik insersi yang strategis, cakupan blok yang luas dapat dicapai hanya dengan satu atau dua titik injeksi tanpa memerlukan infiltrasi yang luas. Artikel ini membahas konsep, mekanisme kerja, serta aplikasi klinis dari blok saraf sensoris sebagai strategi mewujudkan prosedur medis yang minim nyeri. Teknik ini menawarkan *onset* cepat, penggunaan anestesi minimal, serta peningkatan kenyamanan pasien dan efisiensi prosedur. Dengan berbagai manfaat tersebut, pendekatan ini berpotensi menjadi paradigma baru dalam praktik kedokteran modern, khususnya pada berbagai tindakan bedah minor.

Kata kunci: blok saraf sensoris, nyeri prosedural, anestesi lokal, bedah minor

Abstract

Pain during medical procedures remains a major challenge in clinical practice, particularly in minor surgery and simple invasive procedures. Conventional local anesthetic infiltration techniques frequently cause additional pain, tissue distortion, and suboptimal anesthetic distribution, highlighting the need of a simpler, more effective, patient-centered approach. The sensory nerve block targets peripheral sensory nerve branches as distal extensions of the central nervous system. Through strategic selection of insertion points, extensive anesthetic coverage can be achieved with only one or two injection points without the need for extensive tissue infiltration. This article discusses the concept, mechanism of action, and clinical applications of sensoric nerve block as a strategy toward minimally painful medical procedures. This technique offers rapid onset, minimal anesthetic requirements, improved patient comfort, as well as greater procedural efficiency. Given these advantages, this approach has the potential to become a new paradigm in modern medical practice, particularly in various minor surgical procedures.

Keywords: sensory nerve block, procedural pain, local anesthesia, minor surgery

Pendahuluan

Nyeri merupakan salah satu faktor utama yang memengaruhi pengalaman pasien selama menjalani prosedur medis. Pada tindakan bedah minor dan prosedur invasif sederhana, nyeri sering dianggap sebagai konsekuensi yang tidak dapat dihindari. Padahal, ketidaknyamanan selama prosedur dapat berdampak pada kepuasan pasien, tingkat kerja sama pasien, serta efisiensi operator dalam melakukan tindakan.

Teknik anestesi lokal melalui infiltrasi jaringan merupakan metode yang paling umum digunakan dalam praktik klinis, namun teknik ini memiliki beberapa keterbatasan, antara lain nyeri saat penyuntikan, distorsi jaringan, serta distribusi anestesi yang kurang merata. Hal ini dapat mengurangi tingkat presisi tindakan sekaligus meningkatkan ketidaknyamanan pasien.

Seiring dengan perkembangan ilmu kedokteran, muncul kebutuhan akan teknik yang lebih sederhana, efektif, dan mampu memberikan kenyamanan yang lebih baik. Blok saraf sensoris (*sensory nerve block*) menjadi salah satu pendekatan yang menjanjikan karena mampu memberikan efek analgesik yang luas dengan jumlah titik injeksi yang minimal.

Konsep Blok Saraf Sensoris

Blok saraf sensoris (*sensory nerve block*) dalam pendekatan ini menargetkan cabang saraf sensoris perifer sebagai perpanjangan dari sistem saraf pusat yang terletak di area distal. Pendekatan ini berfokus pada titik-titik anatomis strategis, di mana saraf sensoris dapat diakses dengan mudah.

Dengan pemilihan titik insersi yang tepat, cakupan anestesi yang luas dapat dicapai hanya melalui satu atau dua titik injeksi tanpa memerlukan infiltrasi jaringan yang luas. Prinsip ini membedakan pendekatan tersebut dari teknik infiltrasi konvensional yang membutuhkan banyak titik penyuntikan untuk mencapai efek analgesik yang sama. Selain itu, pendekatan ini juga mempertahankan fungsi motorik karena secara selektif menargetkan jalur sensoris.

Mekanisme Kerja dan Keunggulan Blok Saraf Sensoris

Blok saraf sensoris bekerja dengan menghambat transmisi impuls nyeri melalui blok kanal natrium pada saraf perifer. Dengan menghentikan transmisi impuls nyeri sebelum mencapai sistem saraf pusat, teknik ini mampu menghasilkan efek analgesik yang efektif dan terlokalisasi. Selain mekanisme tersebut, pemilihan titik target yang strategis memungkinkan satu titik injeksi mencakup area yang lebih luas dibandingkan teknik infiltrasi konvensional.

Keunggulan utama dari pendekatan ini meliputi:

- Jumlah titik injeksi yang lebih sedikit
- Cakupan area yang lebih luas
- Kebutuhan dosis anestesi minimal
- Onset kerja cepat
- Distorsi jaringan minimal
- Kenyamanan pasien lebih baik
- Peningkatan efisiensi prosedur.

Aplikasi Klinis dari Blok Saraf Sensoris

Blok saraf sensoris dapat diaplikasikan secara luas pada berbagai tindakan bedah minor dan prosedur invasif sederhana, antara lain pada:

1. Area kepala dan wajah

Blok saraf seperti supraorbital, *supratrochlear*, infraorbital, dan mental, mampu memberikan efek analgesik yang efektif untuk berbagai prosedur sederhana pada area kepala dan wajah.

2. Ekstremitas atas

Pendekatan yang menargetkan distribusi saraf palmar memungkinkan cakupan yang luas pada lengan hanya dengan satu atau dua titik injeksi.

3. Ekstremitas bawah

Blok saraf plantar memberikan efek analgesik yang efektif untuk berbagai tindakan pada tungkai dengan teknik yang relatif sederhana.

Simplifikasi Teknik Blok Saraf Sensoris

Pendekatan blok saraf sensoris dirancang sebagai teknik yang sederhana dan praktis untuk diterapkan dalam praktik klinis. Teknik ini dapat dilakukan dengan menggunakan alat dan bahan berikut:

- S spuit 1 ml
- Jarum ukuran kecil
- Anestesi lokal, seperti *lidocaine* atau *levobupivacaine*

Dengan jumlah titik injeksi yang minimal serta penggunaan volume obat anestesi yang kecil, risiko komplikasi dapat diminimalkan dan kenyamanan pasien selama menjalani prosedur dapat ditingkatkan.

Keamanan dan Keterbatasan Blok Saraf Sensoris

Meskipun pendekatan blok saraf sensoris tergolong aman, terdapat beberapa hal yang perlu diperhatikan, yaitu:

- Variasi anatomi antarindividu
- Risiko injeksi intravaskular
- Potensi toksisitas anestesi lokal.

Oleh karena itu, pemahaman anatomi yang baik, teknik injeksi yang tepat, serta penggunaan dosis anestesi yang sesuai sangat penting untuk meminimalkan risiko komplikasi.

Perspektif Masa Depan

Pendekatan blok saraf sensoris memiliki potensi besar dalam mendukung konsep prosedur medis yang minim nyeri. Dengan semakin meningkatnya tuntutan terhadap kenyamanan pasien, teknik ini dapat menjadi standar baru dalam berbagai tindakan bedah minor. Pengembangan lebih lanjut, termasuk integrasi dengan teknologi pencitraan, seperti ultrasonografi, dapat meningkatkan akurasi dan keamanan prosedur. Walaupun demikian, pendekatan berbasis *landmark* tetap memiliki peran penting dalam praktik sehari-hari, terutama di fasilitas kesehatan dengan sumber daya yang terbatas.

Kesimpulan

Blok saraf sensoris merupakan pendekatan yang relatif sederhana namun efektif dalam manajemen nyeri prosedural. Teknik ini mampu memberikan cakupan blok yang luas hanya dengan infiltrasi di satu atau dua titik injeksi. Keunggulan ini menjadikan blok saraf sensoris sebagai alternatif yang lebih efisien dibandingkan teknik konvensional, serta berpotensi menjadi paradigma baru dalam berbagai tindakan bedah minor dan prosedur invasif sederhana.

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Prevalence of Anxiety and Depression in Hemodialysis Patients at RSUP Prof. dr. I.G.N.G. Ngoerah, Denpasar: A Descriptive Study

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Abstract

Background: Patients with chronic kidney disease (CKD) undergoing hemodialysis (HD) often experience substantial physical and psychological burdens, including anxiety and depression. These psychological conditions may adversely affect patients' quality of life and adherence to long-term treatment. Understanding the prevalence of these conditions at RSUP Prof. dr. I.G.N.G. Ngoerah, Denpasar is essential to inform appropriate clinical and psychosocial interventions.

Objective: This study aimed to describe the prevalence and severity levels of anxiety and depression among patients undergoing hemodialysis at RSUP Prof. dr. I.G.N.G. Ngoerah, Denpasar. **Methods:** This descriptive study included 43 patients receiving hemodialysis at RSUP Prof. dr. I.G.N.G. Ngoerah, Denpasar. Data were obtained from medical records and psychological screening using the digitally administered Hospital Anxiety and Depression Scale (HADS). Anxiety and depression levels were categorized as normal (score 0–7), mild (8–10), moderate (11–14), and severe (15–21). **Results:** Among the 43 patients, symptoms of anxiety and/or depression were identified in 23.26% (n=10). Of these, 11.63% (n=5) had mild symptoms, 6.98% (n=3) had moderate symptoms, and 4.65% (n=2) had severe symptoms. The remaining 76.74% (n=33) of patients showed no symptoms of anxiety or depression. **Conclusion:** Anxiety and depression are relatively common among patients undergoing hemodialysis at RSUP Prof. dr. I.G.N.G. Ngoerah, Denpasar. Routine psychological screening and integration of mental health care into hemodialysis management are strongly recommended to improve overall patient well-being and quality of life.

Keywords: chronic kidney disease, hemodialysis, anxiety, depression, Hospital Anxiety and Depression Scale, quality of life, psychosocial support

Abstrak

Latar belakang: Pasien dengan penyakit ginjal kronik (PGK) yang menjalani hemodialisis (HD) sering mengalami beban fisik dan psikologis yang berat, termasuk kecemasan dan depresi. Kondisi psikologis ini dapat berdampak negatif terhadap kualitas hidup pasien serta kepatuhan terhadap pengobatan jangka panjang. Pemahaman mengenai prevalensi kondisi tersebut di RSUP Prof. dr. I.G.N.G. Ngoerah, Denpasar penting untuk merancang intervensi klinis dan psikososial yang tepat. **Objektif:** Penelitian ini bertujuan untuk menggambarkan prevalensi dan tingkat keparahan kecemasan dan depresi pada pasien yang menjalani hemodialisis di RSUP Prof. dr. I.G.N.G. Ngoerah, Denpasar. **Metode:** Penelitian deskriptif ini melibatkan 43 pasien yang menerima terapi hemodialisis di RSUP Prof. dr. I.G.N.G. Ngoerah, Denpasar. Data diperoleh dari rekam medis dan skrining psikologis menggunakan Hospital Anxiety and Depression Scale (HADS) yang diisi secara

digital. Tingkat kecemasan dan depresi dikategorikan sebagai normal (skor 0–7), ringan (8–10), sedang (11–14), dan berat (15–21). **Hasil:** Dari 43 pasien, gejala kecemasan dan/atau depresi ditemukan pada 23,26% (n=10) peserta. Dari jumlah tersebut, 11,63% (n=5) mengalami gejala ringan, 6,98% (n=3) gejala sedang, dan 4,65% (n=2) gejala berat. Sebanyak 76,74% (n=33) pasien tidak menunjukkan gejala kecemasan maupun depresi. **Kesimpulan:** Kecemasan dan depresi relatif sering ditemukan pada pasien yang menjalani hemodialisis di RSUP Prof. dr. I.G.N.G. Ngoerah, Denpasar. Skrining psikologis rutin dan integrasi layanan kesehatan mental ke dalam manajemen hemodialisis sangat dianjurkan untuk meningkatkan kesejahteraan dan kualitas hidup pasien secara keseluruhan.

Kata kunci: penyakit ginjal kronik, hemodialisis, kecemasan, depresi, Hospital Anxiety and Depression Scale, kualitas hidup, dukungan psikososial

Introduction

Chronic kidney disease (CKD) that progresses to end-stage renal disease (ESRD) and requires hemodialysis (HD), places significant physical and psychological burdens on patients. Among the psychological burdens experienced by patients undergoing hemodialysis, anxiety and depression are the most frequently reported conditions, negatively impacting quality of life, reducing treatment outcomes, and even increasing mortality. Despite their clinical significance, these conditions are often underrecognized in routine clinical practice.¹

The prevalence of anxiety and depression among hemodialysis patients varies widely depending on sociocultural context, assessment instruments, and sample characteristics. A study conducted in Lebanon reported a depression prevalence of 40.8% and an anxiety prevalence of 39.6%, with approximately one-quarter of patients experienced both conditions.⁴ A study conducted in Kuwait using the Hospital Anxiety and Depression Scale (HADS) reported that the prevalence of depressive and anxiety symptoms was 21.7% and 21.4%, respectively.¹ Meanwhile, a study from Northern China reported depression in 55.1% and anxiety in 25.9% of patients receiving maintenance hemodialysis.⁵ These variations highlight the importance of locally derived data to accurately estimate the burden of anxiety and depression, and to inform context-appropriate interventions.

In Indonesia, a study conducted during the COVID-19 pandemic at a hospital-based hemodialysis unit in Bekasi found that most patients had normal anxiety levels (84.9%). However, the prevalence of borderline abnormal depression (40.4%) and abnormal depression (23.2%) was substantial, underscoring the need for integrated psychological screening and support within hemodialysis services.² Moreover, a longer duration of hemodialysis has been associated with higher rates of depression, highlighting the importance of ongoing psychological monitoring in clinical practice.²

Methodologically, the Hospital Anxiety and Depression Scale (HADS) is a widely used screening instrument that has been validated in chronic kidney disease and hemodialysis populations to assess anxiety (HADS-A) and depression (HADS-D). The HADS is easily administered, demonstrates good reliability, and is useful for identifying individuals requiring further clinical evaluation, although it is not intended as a definitive diagnostic tool.^{1,3} Its use in hemodialysis populations is further supported by evidence of good validity and widespread application across different languages and cultural settings, making it an appropriate instrument for the initial assessment of psychological disturbances in dialysis services.⁴

Despite the recognized importance of psychological assessment in hemodialysis care, the prevalence and severity of anxiety and depression among hemodialysis patients at RSUP Prof. dr. I.G.N.G. Ngoerah, Denpasar have not been well documented. Therefore, this descriptive study aims to assess the prevalence and severity of anxiety and depression in hemodialysis patients at RSUP Prof. dr. I.G.N.G. Ngoerah, Denpasar using the HADS, as a basis for planning targeted psychosocial interventions.

Methods

This study was a descriptive observational study with a cross-sectional design. Data were collected at a single time point from hemodialysis patients who met the eligibility criteria at RSUP Prof. dr. I.G.N.G. Ngoerah, Denpasar. The study was conducted between July and August 2024. Data sources included medical records, which provided baseline clinical characteristics according to the study protocol, and psychological screening results obtained using the Hospital Anxiety and Depression Scale (HADS). The HADS was administered during routine hemodialysis sessions. This study was design to describe the prevalence and severity of anxiety and/or depression among the hemodialysis patient population, without implementing therapeutic interventions or assessing causal relationships. The inclusion criteria were patients aged ≥ 18 years with end-stage renal disease undergoing hemodialysis at RSUP Prof. dr. I.G.N.G. Ngoerah, Denpasar during the study period, who provided informed consent and were able to complete the HADS independently or with standardized assistance.

The study sample was obtained using a total sampling method, including all hemodialysis patients who were present during the data collection period and met the eligibility criteria, yielding a final sample of 43 patients. All participants received a verbal explanation of the study objectives and provided written informed consent prior to participation. The HADS instrument (14 items; HADS-A for anxiety and HADS-D for depression) was scored according to guidelines and classified into four categories for each subscale: normal (0–7), mild disorder (8–10), moderate disorder (11–14), and severe disorder (15–21).¹⁶

Results

A total of 43 patients participated in this study (**Table 1**). The median age was 51.0 years (range: 21–69 years). More than half of the patients (53.5%) were aged >50 years, while 46.5% were aged ≤ 50 years. The cohort was nearly evenly distributed by sex, with female patients comprising 51.2% and male patients 48.8% of the study population.

The median duration of hemodialysis was 6.0 years (range: 1–17 years). Most patients (53.5%) had undergone hemodialysis for >5 years, while 46.5% had undergone hemodialysis for ≤ 5 years. Regarding hemodialysis frequency, the majority of patients (69.8%) underwent sessions twice weekly, while 30.2% underwent sessions three times weekly. The most common hemodialysis session duration was 4.5 hours (58.1%), followed by 4.0 hours (32.6%) and 5.0 hours (9.3%). Regarding vascular access, the majority of patients used arteriovenous (AV) shunts (81.4%), while 16.3% used a double-lumen central venous catheter (CVC), and 2.3% used femoral vein access.

Table 1. Clinical and demographic characteristics of hemodialysis patients at RSUP Prof. dr. I.G.N.G. Ngoerah, Denpasar

Variables	Frequency (n)	Percentage (%)
Age [median (range)]= 51.0 years (21–69)		
≤50 years	20	46.5
>50 years	23	53.5
Gender		
Male	21	48.8
Female	22	51.2
Duration of hemodialysis [median (range)]= 6.0 years (1–17)		
≤5 years	20	46.5
>5 years	23	53.5
Hemodialysis frequency (session/week)		
2 sessions/week	30	69.8
3 sessions/week	13	30.2
Duration of hemodialysis per session (hours)		
4.0 hours	14	32.6
4.5 hours	25	58.1
5.0 hours	4	9.3
Vascular access		
AV shunts	35	81.4
Double lumen central venous catheter (CVC)	7	16.3
Femoral vein access	1	2.3

The HADS screening results (**Table 2**) revealed that most patients (76.7%) had normal scores on both subscales (HADS-A <8 and HADS-D <8). However, 23.3% of patients were identified as having clinically relevant psychological symptoms, defined as anxiety, depression, or both, defined by HADS-A ≥8 and/or HADS-D ≥8.

Among those with symptoms, 11.6% were in the mild category (HADS score 8–10), 7.0% in the moderate category (11–14), and 4.7% in the severe category (15–21). These findings indicate that although the majority of patients were asymptomatic, nearly one-quarter experienced psychological symptoms of varying severity, highlighting the importance of routine screening and appropriate intervention among patients undergoing hemodialysis.

Table 2. Distribution of anxiety and depression scores based on HADS among hemodialysis patients at RSUP Prof. dr. I.G.N.G. Ngoerah, Denpasar

Variables	Frequency (n)	Percentage (%)
No symptoms [Normal] (HADS-A <8 and HADS-D <8)	33	76.74
Symptoms present (HADS-A ≥8 and/or HADS-D ≥8)	10	23.26
• Mild (8–10)	5	11.63
• Moderate (11–14)	3	6.98
• Severe (15–21)	2	4.65
Total	43	100.0

Note: Of the 43 patients included in the study, 10 (23.26%) were identified as having symptoms of anxiety and/or depression. The mild, moderate, and severe categories represent severity levels within this symptomatic subgroup, while percentages are expressed relative to the total study population (n=43).

Discussion

Prevalence and Severity of Psychological Symptoms (HADS)

In this study, 23.26% of patients were identified as having clinically relevant psychological symptoms, defined as a HADS-A score ≥ 8 and/or a HADS-D score ≥ 8 , while the majority (76.74%) were classified as asymptomatic. Regarding symptom severity, mild symptoms were observed in 11.63% of patients, moderate symptoms in 6.98%, and severe symptoms in 4.65%. These findings were observed in a population predominantly characterized by age >50 years, hemodialysis duration of >5 years, twice-weekly hemodialysis session of 4.5 hours, and arteriovenous fistula or graft (AVF/AVG) as the primary vascular access. Overall, this profile reflects a relatively stable clinical population, with majority psychological symptom morbidity falling within the mild-to-moderate range.

The HADS thresholds applied in this study are consistent with both clinical practice and previous research, in which scores of 0–7 are classified as normal, 8–10 as mild disorder, 11–14 as moderate disorder, and 15–21 as severe disorder. The HADS was self-administered by patients during their hemodialysis sessions. This categorization framework has also been used in a national study conducted during the COVID-19 pandemic, supporting its relevance for mapping symptom severity and identifying patients who may require further psychological follow-up.²

Compared with findings from other settings, the prevalence observed in this study is comparable to that reported in a multicenter study conducted in Kuwait using the HADS, which found prevalence rates of 21.7% for depression, 21.4% for anxiety, and 12.6% for comorbid anxiety and depression.¹ The authors emphasized that the HADS is a screening instrument and that definitive diagnoses should be confirmed through clinical assessment by a mental health specialist.¹

In contrast, a study conducted at a tertiary care center in Lebanon reported considerably higher prevalence rates: anxiety in 39.6% of patients, depression in 40.8%, and comorbid anxiety and depression in 24.1%.⁴ The authors also noted that, in end-stage renal disease (ESRD) populations, some researchers have proposed lower HADS cutoff values than those generally recommended in order to increase screening sensitivity, such as HADS-D ≥ 7 and HADS-A ≥ 6 .⁴ The use of these lower thresholds may substantially affect prevalence estimates and the distribution of symptom severity.⁴

The findings of the present study, which demonstrate a high proportion of patients in the normal category and a predominance of mild disorder over moderate and severe disorder, are consistent with other reports from hemodialysis settings in Indonesia. A study conducted in Bekasi during the COVID-19 pandemic similarly found that most patients had normal anxiety levels, while depression was predominantly observed in the mild and moderate categories, reflecting a symptom distribution comparable to that observed in the present study at RSUP Prof. dr. I.G.N.G. Ngoerah, Denpasar.²

From a clinical perspective, national literature highlights two contrasting patterns. First, adaptation to long-term hemodialysis procedures may mitigate anxiety symptoms in some patients. Second, prolonged hemodialysis duration has been associated with increased depression in some populations, with a higher proportion of depressive symptoms observed among patients receiving hemodialysis for more than 48 months. This findings underscores the importance of individualized, context-sensitive psychological assessment that considers factors such as hemodialysis duration, intradialytic side effects, and the availability of family social support.²

The heterogeneity of prevalence estimates reported across countries, likely reflects differences in patient characteristics, sociocultural contexts, and healthcare system, and the assessment instruments and cutoff values employed. For example, a study from Northern China that employed the Zung Self-Rating Scale reported depression in 55.1% and anxiety in 25.9% of patients receiving maintenance hemodialysis. Variations in measurement tools and cutoff thresholds likely contributed to the higher prevalence rates observed compared with studies using the HADS.⁵

The available evidence highlights the importance of routinely integrating psychological screening into hemodialysis care. The HADS has been widely used and validated in chronic kidney disease and end-stage renal disease populations, and anxiety and depression have been consistently associated with impaired quality of life and adverse clinical outcomes.^{1,3,4} Screening should therefore be followed by referral to mental health professionals for diagnostic confirmation and appropriate intervention, consistent with the principle that the HADS is a screening instrument rather than a diagnostic tool.^{1,3}

The relatively lower prevalence of psychological symptoms observed in this study compared to some international reports, yet comparable to estimates reported from Kuwait, may reflect the stability of the dialysis regimen, the predominance of arteriovenous access (AVF/AVG), and adequate family adaptation and social support. Nevertheless, the presence of patients with moderate and severe disorder remains clinically significant and warrants a standardized referral pathway for further psychiatric evaluation and comprehensive management.¹

Clinical and Demographic Characteristics (Age, Sex, Duration of Hemodialysis, Frequency and Duration of Sessions, Vascular Access)

In this study conducted at RSUP Prof. dr. I.G.N.G. Ngoerah, Denpasar, the majority of patients were aged >50 years (53.5%), with a median of 51.0 years. The sex distribution was relatively balanced, with a slight female preponderance (51.2%). More than half of the patients (53.5%) had undergone hemodialysis for more than 5 years. The most common session frequency was twice weekly (69.8%), with a session duration of 4.5 hours (58.1%). The predominant vascular access was arteriovenous shunts (81.4%), followed by double-lumen central venous catheter (16.3%) and femoral vein access (2.3%). This pattern reflects a clinically stable population with a homogeneous regimen characterized by twice-weekly sessions of 4.0–4.5 hours and predominant use of permanent arteriovenous access.

Compared with a report by Utami *et al.* (2020) from the same institution, the largest age group was 61–80 years, with males comprising the majority (58%), suggesting that our sample was slightly younger and more evenly distributed by sex.⁸ At a hospital in Medan, patient characteristics were also predominantly older adults, with 82% aged >45 years and 58% male; however, hemodialysis duration in that population was mostly less than 12 months, in contrast to our study, which represented a more experienced dialysis population in terms of treatment duration.⁶

The twice-weekly hemodialysis regimen with session duration of 4–5 hours, observed in most patients in this study, is consistent with clinical practice reported in the Indonesian literature. A study conducted at Muhammadiyah Mayong Hospital reported that hemodialysis is commonly performed twice weekly with session durations of 4–5 hours. Additionally, a study from RSUP Prof. dr. I.G.N.G. Ngoerah, Denpasar evaluated hemodialysis adequacy based on a total treatment time of 9–12 hours per week.^{7,8}

The predominance of patients with a hemodialysis duration exceeding 5 years in this study suggests a population with prolonged adaptation to the dialysis procedure. Indonesian clinical literature has highlighted that patient characteristics, including hemodialysis duration and session length, can influence clinical parameters during dialysis.⁷ Consequently, variations in dialysis duration across centers may partly explain the differences in clinical profiles observed across studies.

The predominance of arteriovenous access (AVF/AVG) observed in this study reflects the widespread use of permanent vascular access in long-term hemodialysis programs. Although some local studies have not reported detailed information on vascular access distribution, clinical literature has highlighted that procedural aspects of dialysis, including vascular access type, treatment duration, and intradialytic symptoms, contribute substantially to the overall clinical experience

during hemodialysis.²

Overall, the clinical and demographic profile observed in this study is consistent with those reported among hemodialysis populations across various dialysis centers in Indonesia. The observed differences across studies are largely attributable to variations in age distribution, sex composition, and the duration and regimen of hemodialysis therapy at each center.^{6,7,8}

In this study, psychological symptoms were assessed using the HADS, with scores categorized as normal (0–7), mild disorder (8–10), moderate disorder (11–14), and severe disorder (15–21). The results showed that 23.26% of patients exhibited symptoms of anxiety and/or depression, while the majority (76.74%) were classified within the normal. The distribution of patients across the categories comprised mild disorder in 11.63% of patients, moderate disorder in 6.98%, and severe disorder in 4.65%. The use of these cutoff thresholds allows for an operational distinction between mild symptoms warranting monitoring and moderate-to-severe symptoms requiring further clinical evaluation, consistent with the screening objectives of psychological assessment in hemodialysis services.

Conceptually, the HADS was specifically designed as a self-report instrument to detect symptoms of anxiety and depression among patients with physical illnesses in nonpsychiatric medical populations. It consists of 14 items with separate subscales for anxiety (HADS-A) and depression (HADS-D), each comprising 7 items with scores ranging from 0 to 21.¹¹ This instrument focuses on the nonsomatic components of anxiety and depression, thereby minimizing overlap with the physical symptoms of chronic illness, making it particularly suitable for patients undergoing hemodialysis.^{9,10}

From an operational perspective, the HADS severity grading applied in this study is broadly consistent with European multicenter research practices, which classify scores >10 as abnormal, 8–10 as borderline, and <8 as normal, while confirming good psychometric properties in the dialysis population.⁹ It should be noted that the present study adopted a four-tier classification (normal, mild disorder, moderate disorder, and severe disorder) to provide greater granularity in symptom severity mapping. In the same cohort, approximately one in five patients showed clinical anxiety and one in six patients showed depression, illustrating the utility of the HADS for mapping symptom burden in routine services.⁹

The validity of the HADS in the hemodialysis population has also been evaluated against psychiatric diagnostic interviews. In a validation study conducted in the Netherlands, the HADS-A subscale demonstrated good diagnostic accuracy, with an area under curve (AUC) of 0.95 and an optimal cutoff point of ≥ 10 , a sensitivity of 0.80, and a specificity of 1.00, supporting its suitability for routine dialysis practice.¹⁰ These findings confirm that the HADS-A is efficient for the detection and screening of anxiety in hemodialysis patients, with the added advantage of excluding somatic symptoms common in patients with chronic physical illness.¹⁰

Heterogeneity in HADS cutoff thresholds across dialysis populations warrants consideration, as it may influence prevalence estimates. A study from Lebanon recommended lower cutoff values specifically for patients with end-stage renal disease, namely HADS-D ≥ 7 and HADS-A ≥ 6 , to optimize the balance between sensitivity and specificity, alongside the generally recommended cutoff of ≥ 8 for broader medical settings.⁴ The same study also provided a clear operational framework for categorizing symptom severity for routine clinical use.⁴

In the national context, the HADS has been implemented in hemodialysis units in Indonesia using a three-tier classification: normal (0–7), borderline (8–10), and clinically significant (≥ 11), to map the burden of anxiety and depression during the COVID-19 pandemic, supporting the operational suitability of this instrument in dialysis settings.² The present study

extended this framework by adopting a four-tier classification to provide greater granularity in symptom severity mapping. The HADS functions as a screening instrument rather than a diagnostic tool, a distinction that must be maintained in clinical practice. Definitive diagnosis requires a structured clinical interview conducted by an experienced clinician, such as the Structured Clinical Interview for DSM (SCID). Positive screening results should be followed by appropriate referral for diagnostic confirmation and treatment.⁴ Accordingly, the implementation of the HADS in hemodialysis units can be incorporated into routine care pathways for early detection, periodic monitoring, and identification of patients requiring psychological intervention. This approach should incorporate cutoff thresholds appropriate for local population characteristics and aligned with the specific screening objectives of the dialysis service.^{9,10,11}

The Need for Routine Screening and Integrated Psychosocial Referrals

The findings of this study indicate that approximately one in four hemodialysis patients at RSUP Prof. dr. I.G.N.G. Ngoerah, Denpasar have psychological symptoms based on HADS (23.26%), while the majority are in the normal category. The severity distribution was predominantly mild disorder, with a relatively small proportion reaching moderate or severe disorder. Clinically, this pattern supports the need for routine screening to ensure that patients with mild-to-moderate symptoms are not overlooked, as well as for an integrated psychosocial referral pathway for patients scoring at or above the HADS cutoff applied in this study.

Externally, the need for routine psychological screening is further supported by service policies. A systematic review of patients with kidney failure highlighted that the End-Stage Renal Disease Quality Incentive Program incorporates routine depression screening as a quality indicator. However, because standardized protocols are lacking across facilities, the development of clear local standard operating procedures is essential.¹²

Instrument selection requires careful consideration of validity, ease of use, and implementation implications. In this study, HADS was employed and is appropriate for populations with chronic disease. Comparative research has indicated that the Beck Depression Inventory-II (BDI-II) is the most extensively studied instrument; however, its use entails a cost per administration, which may limit practicality in routine healthcare settings. Brief, public-domain instruments such as the PHQ-9 and GDS-15 (for elderly populations) have demonstrated good performance, although supporting evidence remains limited.¹² Moreover, variations in cutoff thresholds and methodological differences across studies underscore the importance of confirming positive screening results prior to treatment decisions, to minimize the risk of misclassification and overtreatment.¹²

Technical implementation aspects are also important. Depression scores may be inflated when screening is performed during dialysis sessions due to somatic symptom overlap. Therefore, screening outside of the dialysis schedule is preferred to reduce somatic bias.¹² Furthermore, because policies mandate follow-up after a positive screening, brief tools may serve as an initial screening step before a comprehensive assessment or clinical confirmation.¹²

At the systems level, a national consensus in the United Kingdom recommends holistic wellbeing assessment for all individuals with chronic kidney disease (CKD) entering dialysis or the transplant waitlist. This includes the use of validated measurement tools, integration of screening results into routine monitoring systems, and referral to psychological or psychiatric services, counseling, social work, or liaison psychiatry where needs are identified.¹³ The recommendations also advocate for annual screening of populations undergoing or planning dialysis, as well as the use of digital resources and capacity building for healthcare workers to identify and address psychosocial needs.¹³ The Kidney Disease: Improving Global Outcomes (KDIGO) 2024 guidelines identify depression as a priority patient-reported outcome within the quality of life domain and recommend evidence-based symptom management strategies to support patients living with CKD within a supportive care framework, including management of emotional

and psychological distress.¹⁴

Evidence from a randomized trial of the Kidney Optimal Health Program in advanced CKD demonstrated significant reductions in depression at 12 months compared with usual care, with high program acceptability, supporting the integration of structured psychosocial interventions into routine care for patients with positive screening results.¹⁵

Strengths and Limitations of the Study

This study has several methodological strengths. First, it provides a previously unreported local baseline estimate of the burden of anxiety and depression among hemodialysis patients at RSUP Prof. dr. I.G.N.G. Ngoerah, Denpasar, providing a foundation for future psychosocial interventions and service policies. Second, the use of the standard HADS with clearly defined severity categories (normal, mild, moderate, severe) enhanced measurement consistency and facilitated clinical interpretation. Third, the total sampling method, which included all eligible patients present during the study period, minimized selection bias arising from nonsystematic sampling. Fourth, data collection reliability was strengthened through standardized HADS administration procedures, enumerator training, limited pilot testing, cross-validation of medical record data, and anonymization of participant information.

This study also has several limitations that should be considered when interpreting the findings. The cross-sectional design captures conditions at a single point in time, precluding the assessment of symptom dynamics over time or causal relationships with clinical factors such as hemodialysis duration, dialysis adequacy, comorbidities, and ongoing therapy. The relatively small sample size (n=43) and single-center setting, limit the generalizability of the results to broader populations. As measurements were conducted using a self-report questionnaire, there remains the potential for information bias due to mood at the time of administration, fatigue, or limited reading comprehension assistance, affecting item interpretation. Additionally, administration of the HADS during dialysis visits may have been influenced by procedure-related somatic symptoms. Although the HADS was designed to minimize somatic elements, residual somatic bias cannot be entirely excluded in some patients.

As the HADS was used as a screening instrument, clinical diagnoses were not established, and results cannot be compared with formal psychiatric diagnoses. Furthermore, the focus on a composite “symptoms present” status and the distribution across severity categories did not allow for detailed separation of anxiety and depression profiles by subscale, which may obscure differences in intervention needs across each domain. Finally, the choice of HADS cutoff thresholds has the potential to influence prevalence estimates; variations in proposed cutoff values across different hemodialysis populations may result in different figures when applied to this cohort.

The implications of this study are best understood as a foundational baseline to encourage routine screening and to strengthen psychosocial referral pathways in hemodialysis units. Further studies are recommended using larger, multicenter samples, conducting repeated measurements outside dialysis sessions to reduce timing bias, analyzing the HADS-A and HADS-D subscales separately, and considering diagnostic confirmation with a standardized clinical interview. This approach would improve the accuracy of burden estimates, clarify intervention targets, and strengthen the external validity of the findings.

Conclusion

This descriptive study provides an initial overview of the psychological status of hemodialysis patients at RSUP Prof. dr. I.G.N.G. Ngoerah, Denpasar. Of the 43 patients studied, 23.26% were identified as having symptoms of anxiety and/or depression based on HADS screening, while 76.74% were classified as asymptomatic. The severity

distribution comprised mild disorder in 11.63% of patients, moderate disorder in 6.98%, and severe disorder in 4.65%. The study population was predominantly characterized by age >50 years, hemodialysis duration exceeding 5 years, a twice-weekly regimen with sessions of 4.5 hours, and arteriovenous access (AVF/AVG) as the predominant vascular access. Within this population, the overall burden of psychological symptoms was relatively low, although clinically significant subgroups requiring further evaluation were identified.

These findings support the use of the HADS as a practical and informative screening tool for the early assessment of anxiety and depression in hemodialysis services. Furthermore, they provide an operational basis for implementing routine, documented psychological screening, establishing clear follow-up thresholds, and strengthening integrated psychosocial referral pathways to psychology, psychiatry, counselling, and social support services. Considering the limitations of cross-sectional design, sample size, and single-center setting, the findings of this study serve as a local baseline for program planning, service quality improvement, and patient and family education.

Future research with larger sample sizes, multicenter designs, and repeated measurements outside dialysis sessions is needed to improve external validity, monitor longitudinal symptom dynamics, and evaluate the effectiveness of psychosocial interventions. Separate analyses of the HADS-A and HADS-D subscales, along with diagnostic confirmation using a standardized clinical interview, are also recommended to ensure accurate identification and management. Overall, these findings support the strengthening of psychosocial screening and referral policies in the hemodialysis unit of RSUP Prof. dr. I.G.N.G. Ngoerah, Denpasar, with the aim of improving quality of life and treatment adherence among hemodialysis patients.

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Disclosure

The authors declare that there is no conflict of interest related to this research. This study was conducted independently and did not receive financial support from industry or commercial sponsors.

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Insufisiensi Adrenal Tersier pada Penggunaan Steroid Jangka Panjang

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Abstrak

Insufisiensi adrenal merupakan suatu kondisi yang dapat mengancam jiwa, yang secara tersier dapat disebabkan oleh penggunaan steroid jangka panjang. Pemberian steroid pada pasien dengan artritis gout biasanya diberikan secara kronis, namun sering tanpa pengawasan medis yang memadai, sehingga menyebabkan lingkaran patogenesis insufisiensi adrenal akibat gangguan mekanisme umpan balik negatif kortisol pada aksis hipotalamus-hipofisis-adrenal. Hal tersebut menyebabkan respons kortisol yang inadekuat, sehingga memungkinkan timbulnya gejala klinis insufisiensi adrenal, dan dapat menyebabkan krisis adrenal yang fatal. Pada kasus ini dilaporkan seorang pasien laki-laki usia produktif dengan riwayat artritis gout yang mengalami insufisiensi adrenal. Pasien datang dengan gambaran klinis *cushingoid* dan kondisi imunodefisiensi sekunder, bahkan disertai kondisi krisis adrenal. Manajemen kondisi akut telah dilakukan, meskipun data untuk diagnosis berupa kadar kortisol plasma yang rendah baru terkonfirmasi setelah pasien keluar dari rumah sakit. Penggunaan steroid yang tidak bijaksana dan tanpa pengawasan yang memadai masih menjadi permasalahan medis di tengah masyarakat. Skrining yang tidak adekuat terkait hal ini juga masih menjadi masalah yang belum teratasi. Pengenalan dini gejala dan tanda klinis insufisiensi adrenal akibat penggunaan steroid menjadi hal yang esensial, untuk memastikan tata laksana awal yang tepat dan cepat.

Kata kunci: kortisol plasma, krisis adrenal, penggunaan steroid, *cushingoid*

Abstract

Adrenal insufficiency is a life-threatening condition that may occur as a tertiary effect of long-term use of steroids. Steroid use in patients with gout arthritis is often administered chronically. However, without adequate medical supervision, it can cause a pathogenic loop of adrenal insufficiency through disruption of the cortisol negative feedback mechanism on the hypothalamic-pituitary-adrenal axis. This disruption leads to an inadequate cortisol response, allowing clinical symptoms of adrenal insufficiency to develop, and a fatal adrenal crisis could emerge. In this case, we reported a productive-aged man with underlying disease of gout arthritis who developed adrenal insufficiency. The patient presented with *cushingoid* clinical features and a secondary immunodeficiency state, with suspected adrenal crisis. Management of the acute condition was carried out, although the diagnostic confirmation of low plasma cortisol levels was only obtained after the patient had been discharged from the hospital. The inappropriate and unsupervised use of steroid remains a medical problem in our society. Inadequate screening related to this issue is still an unmet obstacle. Early recognition of the clinical signs and symptoms of steroid-induced adrenal insufficiency is essential to ensure timely and appropriate management.

Keywords: plasma cortisol, adrenal crisis, steroid use, *cushingoid*

Pendahuluan

Insufisiensi adrenal (IA) merupakan suatu kondisi yang dapat mengancam jiwa akibat respons kortisol yang tidak memadai.

Kondisi ini mungkin memerlukan terapi substitusi glukokortikoid seumur hidup, bahkan dapat memicu tercetusnya krisis adrenal. Jumlah individu dengan insufisiensi adrenal primer dan sekunder di Eropa diperkirakan sekitar 20–50 per 100.000 orang.¹ Insufisiensi adrenal tersier akibat penggunaan obat, salah satunya karena penggunaan steroid jangka panjang tanpa pengawasan yang memadai, sering terlewatkan karena tanda dan gejala yang bersifat nonspesifik serta tidak dapat dibedakan dari manifestasi kondisi yang mendasarinya.^{2,3,4} Bukti saat ini, termasuk uji klinik acak dan studi observasional, menunjukkan adanya variasi substansial antarpasien, baik dalam hal risiko maupun perjalanan klinis insufisiensi adrenal yang diinduksi glukokortikoid, meskipun kedua hal tersebut saat ini belum dapat diprediksi.⁴

Konsumsi steroid jangka panjang pada pasien dengan penyakit reumatologi kronis berpotensi menimbulkan permasalahan sistemik dan bersifat fatal pada pasien karena pengawasan terhadap penggunaan steroid jangka panjang yang masih belum adekuat. Sekitar 7 dari 1.000 orang diresepkan terapi kortikosteroid oral jangka panjang. Diperkirakan 100 kali dari angka kejadian tersebut dapat mengalami defisiensi intrinsik kortisol, sehingga menciptakan populasi yang berisiko mengalami krisis adrenal. Pada pasien dengan insufisiensi adrenal primer maupun sekunder akibat penyakit adrenal dan hipotalamus hipofisis, krisis adrenal yang membutuhkan perawatan di rumah sakit terjadi pada sekitar 6–8 per 100 pasien per tahun.⁵ Steroid dengan rute pemberian oral dan intraartikular, serta durasi pengobatan jangka panjang dan dosis tinggi, memiliki risiko terbesar terhadap kejadian insufisiensi adrenal yang diinduksi glukokortikoid yang dapat ditegakkan melalui pemeriksaan biokimia. Terlebih, tidak terdapat cara pemberian, durasi pengobatan, atau dosis pemberian yang bebas dari risiko.⁴

Pedoman klinis berbasis bukti untuk mendukung manajemen atau pencegahan klinis insufisiensi adrenal akibat steroid masih belum disusun secara sistematis.⁴ Prediktor insufisiensi adrenal yang diinduksi oleh glukokortikoid meliputi pengobatan dosis tinggi dalam jangka panjang. Hingga saat ini, implikasi klinis spektrum yang lengkap dan khas belum dapat dijelaskan sepenuhnya, bahkan terkesan mirip dengan kondisi imunodefisiensi lainnya.^{4,6} Studi kasus ini membahas mengenai insufisiensi adrenal pada seorang laki-laki usia produktif dengan imunodefisiensi dan ketidakseimbangan hemodinamik. Kondisi tersebut dicurigai sebagai komplikasi dari insufisiensi adrenal yang disebabkan oleh infeksi akut akibat penyalahgunaan kortikosteroid jangka panjang. Kasus ini menunjukkan bahwa skrining terhadap gangguan endokrin di fasilitas kesehatan masih rendah, padahal penggunaan steroid jangka panjang cukup sering ditemukan.

Ilustrasi Kasus

Seorang pasien laki-laki berusia 38 tahun datang ke Rumah Sakit Umum Pusat (RSUP) Prof. dr. I.G.N.G Ngoerah, Denpasar pada tanggal 27 November 2022 dengan keluhan luka pada kedua lutut dan kaki. Nyeri dan luka pada kedua lutut dan kaki dirasakan sejak kurang lebih 3 bulan sebelum masuk rumah sakit. Luka diawali dengan pembengkakan dan teraba keras pada lutut dan jempol kaki kanan dan kiri pasien. Sekitar satu bulan sebelum masuk rumah sakit, pembengkakan tersebut semakin membesar dan meluas disertai dengan kemerahan. Nyeri yang dirasakan juga semakin parah, sehingga pasien hanya dapat berbaring di tempat tidur.

Keluarga biasanya merawat sendiri luka pada kaki kanan dan kiri pasien di rumah dengan cara dikompres. Satu hari sebelum masuk rumah sakit, pembengkakan pada kedua lutut pecah dan keluar nanah bercampur darah. Keluarga pasien kemudian menutup luka tersebut dengan kasa dan membawa pasien ke unit gawat darurat RSUP Prof. dr. I.G.N.G Ngoerah, Denpasar. Keluhan serupa pernah dialami pasien beberapa kali sejak kurang lebih satu tahun sebelumnya, namun pembengkakan hanya sampai bernanah dan belum pernah pecah menjadi luka, kemudian membaik dengan sendirinya tanpa dibawa ke rumah sakit.

Pasien juga mengeluhkan lemas, mual, dan nyeri ulu hati sejak satu hari sebelum masuk rumah sakit. Nyeri ulu hati dirasakan bertambah berat saat pasien makan. Pasien juga merasakan mual sejak pagi sebelum masuk rumah sakit,

tetapi tidak disertai muntah. Buang air besar (BAB) dengan konsistensi cair tanpa adanya lendir atau darah sebanyak 4 kali dalam 2 hari sebelum masuk rumah sakit. Keluhan tersebut membaik sejak satu hari sebelum masuk rumah sakit. Pasien juga pernah mengalami BAB berdarah kurang lebih dua tahun sebelumnya, dan menjalani perawatan di rumah sakit serta mendapatkan transfusi darah sebanyak 4 kantong. Pasien tidak pernah mengeluhkan hal serupa setelahnya hingga saat ini. Selain itu, pasien juga melaporkan adanya kencing berwarna merah seperti teh sejak sekitar beberapa bulan sebelum masuk rumah sakit. Keluhan demam, batuk, dan sesak disangkal oleh pasien.

Pasien mengeluhkan bengkak pada sendi-sendi jari tangan dan kaki yang dialami sejak beberapa tahun belakangan, dengan kondisi terberat pada tumit kaki kanan. Pembengkakan pada tumit kanan tersebut disertai luka terbuka yang mengeluarkan nanah dan rembesan darah. Bengkak pada sendi jari tangan dan kaki dirasakan muncul secara perlahan dan semakin mengganggu karena pasien tidak dapat menggenggam atau berjalan dengan baik. Nafsu makan pasien menurun karena adanya nyeri yang dirasakan. Keluhan seperti perdarahan di tempat lain disangkal.

Pasien memiliki riwayat asam urat (*gout arthritis*) sejak sekitar 5 tahun sebelumnya, dengan benjolan baru yang sering muncul dan bernanah serta hilang timbul di beberapa tempat. Riwayat penyakit sistemik kronis lain seperti kencing manis (diabetes melitus), hipertensi, dan penyakit autoimun disangkal oleh pasien. Pasien mengalami penurunan berat badan yang tampak dari tubuh yang semakin kurus, dan pakaian yang terasa longgar sejak sekitar satu tahun sebelumnya. Namun, pasien dan keluarganya tidak dapat memastikan besarnya penurunan berat badan yang telah terjadi. Pasien juga mengeluhkan pembengkakan wajah yang semakin progresif dan penipisan rambut yang dirasakan sejak satu tahun sebelumnya.

Pasien sering mengonsumsi antinyeri (*piroxicam*), steroid (*dexamethasone*), dan jamu herbal secara rutin sejak 6 bulan sebelum masuk rumah sakit untuk mengatasi nyeri persendian yang dirasakan. Obat-obatan tersebut dibeli oleh pasien secara berkala di apotek terdekat secara bebas tanpa resep dari dokter. *Dexamethasone* diminum oleh pasien hingga tiga kali sehari sebanyak satu tablet secara berturut-turut setiap hari selama 6 bulan sampai saat pasien masuk rumah sakit. Istri pasien menambahkan bahwa pasien sudah sering membeli *dexamethasone* sendiri sejak pertama kali menderita sakit asam urat (*gout arthritis*) sekitar 5 tahun lalu, namun penggunaannya menjadi rutin sejak sekitar 6 bulan terakhir.



Gambar 1. Kondisi klinis pasien

A. Foto klinis pasien dari arah depan, tampak pasien dengan wajah *cushingoid* (*moon face*) dan alopesia

B. Tampak jari-jari tangan pasien dengan *tophus* multipel

C. Tampak kedua ekstremitas inferior pasien dengan *tophus* dan ulkus multipel yang berisi pus

Pasien merupakan seorang sopir bus pariwisata dan sekujur tubuhnya dipenuhi tato. Pasien juga gemar mengonsumsi alkohol hampir setiap hari sejak berusia belasan tahun. Volume alkohol yang dikonsumsi semakin bertambah pada akhir pekan, di mana pasien dapat meminum lebih dari dua botol alkohol. Pasien juga gemar merokok, dengan konsumsi rokok sebanyak 4–5 batang per hari sebelum sakit.

Pasien kemudian diperiksa di unit gawat darurat (triase medis) dengan kondisi hipotensi (tekanan darah 90/60 mmHg), nadi teraba lemah dengan frekuensi 105 kali per menit, laju napas 24 kali per menit, saturasi oksigen 97% pada udara ruangan, suhu badan 36,1°C, dan skor *visual analogue score* (VAS) 7/10. Pemeriksaan status generalis menemukan karakteristik wajah *moon face* (**Gambar 1.A**), serta oral-esophageal kandidiasis. Pemeriksaan status jantung, paru, dan abdomen menunjukkan hasil dalam batas normal.

Status lokalis pada kedua tangan (*regio manus dekstra dan sinistra*) menunjukkan hasil: *look: tophus* (+), *edema* (+), *feel: tenderness* (+), *move: aktif dan pasif terbatas nyeri*. Status lokalis pada kedua kaki (*regio pedis dekstra dan sinistra*) menunjukkan: *look: tophus* (+), *edema* (+), *eritema* (+), *feel: tenderness* (+), *move: aktif dan pasif terbatas nyeri*. *Regio genu dekstra: look: tampak tophus multipel, luka terbuka, ulkus* (+), *pus* (+), *perdarahan aktif* (-), *feel: nyeri* (+) teraba keras pada *tophus*, *move: range of movement* terbatas nyeri. *Regio genu sinistra: look: tampak tophus multipel, luka terbuka, ulkus* (+), *pus* (+), *perdarahan aktif* (-), *feel: nyeri* (+) teraba keras pada *tophus*, *move: range of movement* terbatas nyeri.

Skor American College of Rheumatology–The European League Against Rheumatism (ACR-EULAR) pada pasien ini adalah 12, dengan rincian pola keterlibatan sendi (2), karakteristik episode (2), ditemukan *tophus* (4), asam urat

13,92 mg/dl (4). Skor *functional class gout arthritis* pada pasien disimpulkan berada pada *functional class IV* karena pasien tetap melaporkan rasa nyeri, meski telah beristirahat dan berbaring.

Hasil pemeriksaan penunjang menunjukkan kondisi hipoglikemia saat pasien pertama kali diperiksa di unit gawat darurat RSUP Prof. dr. I.G.N.G. Ngoerah, Denpasar, dengan kadar gula darah sebesar 63 mg/dl, yang kemudian membaik menjadi 135 mg/dl setelah pasien minum teh manis hangat di triase medis. Pemeriksaan darah lengkap yang dilakukan pada tanggal 26 November 2022 saat pasien masih di triase medis menunjukkan leukositosis dengan dominan neutrofil. Adapun rinciannya sebagai berikut: sel darah putih (*white blood cell/WBC*) $16,30 \times 10^3/\text{mcl}$; jumlah neutrofil absolut (*absolute neutrophil count/ANC*) $14,31 \times 10^3/\text{mcl}$; hematocrit (*hematocrit/HCT*) 31,50 %; hemoglobin (Hb) 10,30 g/dl; *mean corpuscular volume* (MCV) 81,40 fl; *mean corpuscular hemoglobin* (MCH) 26,6 pg; trombosit $717 \times 10^3/\text{mcl}$.

Hasil pemeriksaan laboratorium lainnya menunjukkan kadar albumin sebesar 2,16 g/dl dan natrium serum 128 mmol/l. Pada pemeriksaan urinalisis, tidak ditemukan adanya leukosit sedimen dan nitrit. Pasien menunjukkan adanya imunodefisiensi secara klinis sehingga dilakukan pemeriksaan *anti-human immunodeficiency virus* (anti-HIV) dengan hasil nonreaktif. Dari pemeriksaan kultur dasar luka, ditemukan isolasi bakteri *Staphylococcus aureus* yang signifikan sebagai penyebab infeksi pasien, di mana *ciprofloxacin* dapat dipertimbangkan sebagai pilihan terapi antibiotik.



Gambar 2. Hasil radiologi ekstremitas bawah

A. Foto *ankle sinistra AP/lateral*, tampak lesi litik destruktif disertai erosi pada tulang metatarsal hingga *phalang distal digiti I pedis sinistra* dengan gambaran *rat bite appearance*

B. Foto *pedis sinistra AP/oblique*, tampak lesi litik dan *rat bite appearance*, mengesankan gambaran *gout arthritis* dengan infeksi sekunder

Hasil pemeriksaan radiologi toraks AP dalam batas normal, sedangkan foto polos abdomen pasien menunjukkan suspek nefrolitiasis bilateral dan vesikolitiasis. Tidak tampak gambaran ileus maupun pneumoperitoneum. Pada hasil pemeriksaan USG abdomen, ditemukan nefrolitiasis ginjal kanan kiri multiple serta *septated gall bladder*, sedangkan pada hepar, lien, pankreas, buli, dan prostat tidak tampak kelainan. Hasil pemeriksaan foto *ankle sinistra AP/lateral* dan *pedis sinistra AP/olique* memberikan gambaran *gout arthritis* dengan infeksi sekunder (**Gambar 2.A dan 2.B**).

Penanganan awal pasien berupa pemberian *intravenous fluid drip* (IVFD) NaCl 0,9% *loading* 1.000 ml. Tekanan darah pasien kemudian membaik menjadi 100/60 mmHg dengan nadi 92 kali/menit yang reguler dan teraba adekuat. Terapi dilanjutkan dengan pemberian IVFD D5% 30 tetes per menit untuk pemeliharaan. Pemeriksaan gula darah acak pasien yang sempat menunjukkan kondisi hipoglikemia (76 mg/dl) dikoreksi dengan pemberian teh hangat manis per oral; gula darah acak pasien kemudian membaik menjadi 163 mg/dl. Pasien mendapatkan terapi antibiotik intravena spektrum luas, serta dikonsulkan ke bagian tropik infeksi, endokrinologi, gastrohepatologi, bedah urologi, dan dilakukan tata laksana *source control* bersama sejawat bedah trauma, di mana steroid belum diberikan.

Pasien juga menunjukkan kondisi klinis terjadinya imunodefisiensi, sehingga dilakukan pemeriksaan serologis anti-*human immunodeficiency virus* (anti-HIV) pada tanggal 28 November 2022 (hari pertama perawatan di bangsal rumah sakit) dengan hasil nonreaktif. Selain itu, hasil pemeriksaan serologis penanda virus seperti HBsAg dan anti-HCV juga menunjukkan hasil nonreaktif. Diagnosis pasien kemudian berkembang menjadi syok hipovolemik akibat suspek kehilangan cairan dan kurangnya asupan (*intake*) yang telah membaik, hipoglikemia akibat suspek kurangnya *intake* (terkoreksi), *acute on chronic gout arthritis pedis dextra functional class IV*, *tophus* terinfeksi disertai sepsis, hiperurisemia, selulitis dd/erisipelas, suspek gastropati akibat obat antiinflamasi nonsteroid (OAINS) dengan riwayat hematokezia. Pasien juga didiagnosis dengan suspek sindrom *Cushing* dan hiponatremia kronis asimtomatik hipovolemik-hipoosmolar yang diduga akibat kehilangan cairan dan asupan yang kurang. Selain itu, ditemukan hipoalbuminemia yang diinduksi oleh inflamasi kronis, kemungkinan gangguan sirkulasi atau habisnya cadangan albumin karena kondisi sepsis berat. Diagnosis lain meliputi nefrolitiasis dan vesikolitiasis, observasi adanya hematuria yang disebabkan suspek batu saluran kemih, serta oral esophageal kandidiasis.

Pasien menjalani perawatan selama tujuh hari di ruang rawat inap. Pada hari pertama perawatan di ruang Lely, pasien mulai mendapatkan steroid intravena. *Methylprednisolone* diberikan dengan dosis awal 62,5 mg tiap 24 jam secara intravena selama tiga hari. Dosis *methylprednisolone* pada pasien kemudian diturunkan setelah hari ketiga menjadi sebesar 16 mg tiap 12 jam melalui rute oral. Hasil pemeriksaan kadar kortisol plasma pasien pada pagi hari yang diambil sekitar 3 hari setelah pasien dinyatakan dalam perawatan mendapatkan hasil <1 mcg/dl (<27,6 nmol/l), yang menunjukkan kondisi insufisiensi adrenal.

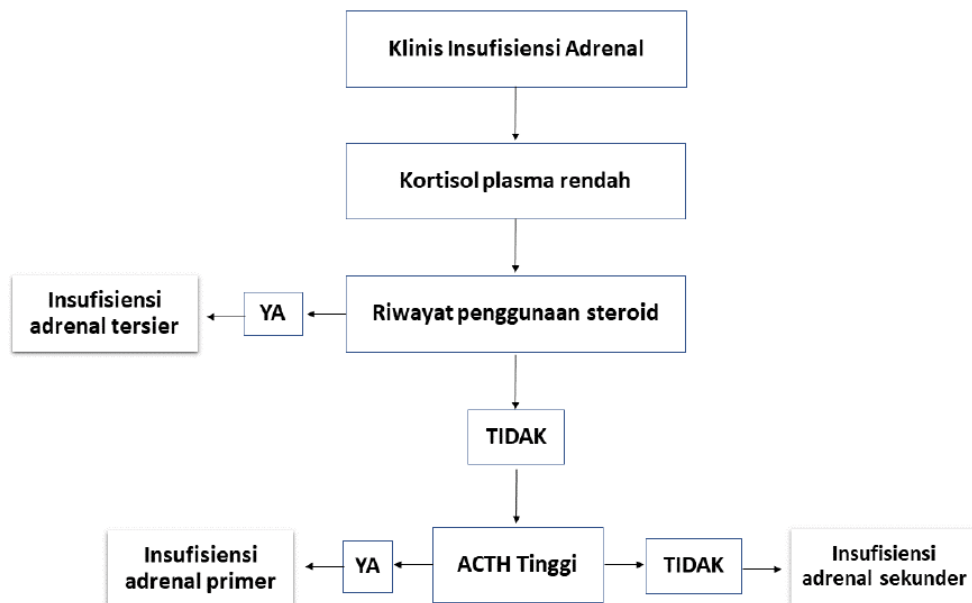
Mobilisasi bertahap, perawatan luka berkala, serta tata laksana nutrisi bersama dengan spesialis kedokteran gizi klinis telah dilakukan. Kondisi klinis pasien menunjukkan perbaikan pada hari kelima perawatan. Pemberian antibiotik intravena selama lima hari kemudian diganti menjadi sediaan oral. Pasien dinyatakan dapat menjalani perawatan poliklinik pada hari rawat ketujuh, dengan seluruh terapi telah diganti menjadi sediaan oral, serta direncanakan penegakkan diagnosis dan tata laksana lanjutan secara rawat jalan.

Diskusi

Insufisiensi adrenal (IA) merupakan kondisi yang dapat mengancam jiwa, yang membutuhkan terapi substitusi glukokortikoid (GC) seumur hidup, serta adaptasi stres untuk mencegah terjadinya krisis adrenal. Jumlah individu dengan insufisiensi adrenal primer dan sekunder di Eropa diperkirakan mencapai 20–50 per 100.000 orang.¹ Insufisiensi adrenal adalah kondisi umum dengan banyak penyebab, yang dapat dibagi menjadi jenis primer (adrenal), sekunder (hipofisis), dan tersier (hipotalamus) (**Gambar 3**).³ Setiap jenis insufisiensi adrenal memiliki etiologi yang berbeda dengan implikasi terhadap tata laksana dan tindak lanjut. Insufisiensi adrenal primer terjadi lebih jarang daripada insufisiensi adrenal sekunder atau tersier. Kondisi ini disebabkan oleh patologi intrinsik kelenjar adrenal, seperti autoimunitas yang umumnya merusak atau adanya kelainan steroidogenesis bawaan. Insufisiensi adrenal sekunder jarang terjadi dan muncul karena adanya defek fungsi kelenjar hipofisis yang sering kali disebabkan oleh adenoma hipofisis atau efek terapi. Sementara itu, insufisiensi adrenal tersier yang disebabkan oleh terapi steroid eksogen merupakan bentuk umum dari insufisiensi adrenal. Kondisi ini sering terlewatkan karena tanda dan gejalanya bersifat nonspesifik sehingga tidak dapat dibedakan dari manifestasi kondisi yang mendasarinya.²

Pada kasus ini, pasien dengan penyakit dasar *gout arthritis* disertai *tophus* multipel yang mengalami infeksi sekunder berupa luka bernanah pada ekstremitas bawah, datang dengan kondisi klinis hipotensi, hipoglikemia, *moon face*, alopesia, penurunan berat badan, serta keluhan nonspesifik lain seperti diare, nyeri ulu hati, dan penurunan nafsu makan. Pasien menunjukkan gejala *immunocompromised*. Setelah ditelusuri lebih lanjut, penyebab imunodefisiensi sekunder akibat infeksi virus dapat dieksklusi. Riwayat konsumsi steroid jangka panjang tanpa disertai pemantauan medis mengarahkan

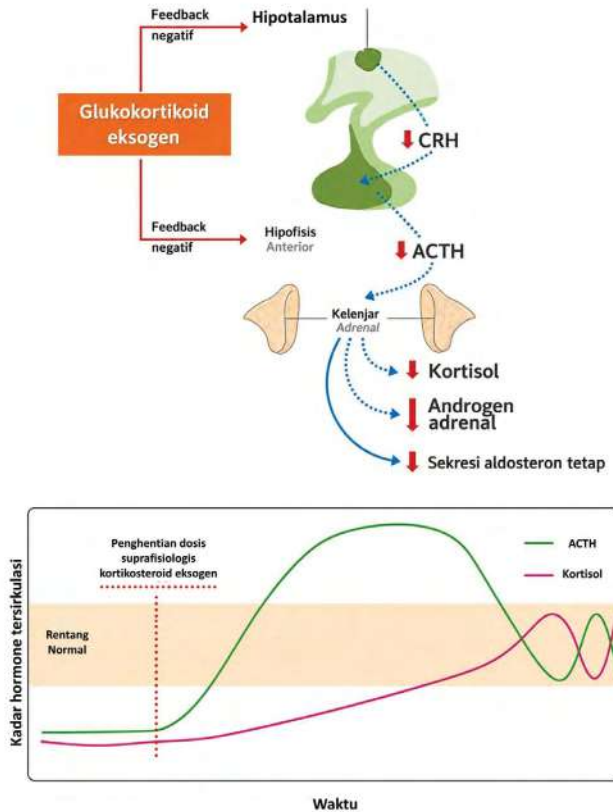
keluhan pasien kepada kondisi insufisiensi adrenal tersier yang dikonfirmasi dengan hasil pemeriksaan kortisol plasma.



Gambar 3. Algoritma diagnosis insufisiensi adrenal pada orang dewasa³

Alur penegakkan diagnosis kondisi insufisiensi adrenal dapat dilihat pada **Gambar 3**. Penegakan diagnosis ini bergantung pada tingkat kegagalan respons adrenokortikal terhadap *adrenocorticotrophic hormone* (ACTH). Kadar kortisol plasma yang menurun dan hilangnya ritme diurnal merupakan langkah awal. Selanjutnya, penegakkan diagnosis dapat dilanjutkan melalui pemeriksaan kadar ACTH plasma yang meningkat.⁷ Apabila ditemukan kadar kortisol plasma yang rendah diikuti dengan riwayat penggunaan steroid jangka panjang maka diagnosis insufisiensi adrenal tersier dapat ditegakkan,³ seperti pada kasus ini. Kadar kortisol plasma pagi kurang dari 83 nmol/l merupakan parameter untuk penegakkan diagnosis insufisiensi adrenal sekunder maupun tersier.³ Dalam kasus ini, kadar plasma kortisol pasien sebesar <1 mcg/dl (<27,6 nmol/l), yang mengonfirmasi penegakkan diagnosis insufisiensi adrenal.

Patofisiologi Insufisiensi Adrenal Tersier akibat Steroid



Gambar 4. Patofisiologi supresi dan pemulihan (*recovery*) aksis hipotalamus-hipofisis-adrenal (*hypothalamic-pituitary-adrenal/HPA*) yang diinduksi glukokortikoid¹²

Insufisiensi adrenal dikategorikan menurut mekanisme yang mendasari, yaitu: (1) insufisiensi adrenal primer, menunjukkan adanya penyakit adrenal dan biasanya disertai dengan penurunan kadar aldosteron; (2) insufisiensi adrenal sekunder, melibatkan defisiensi hormon adrenokortikotropik (*adrenocorticotrophic hormone/ACTH*) yang timbul akibat gangguan hipofisis; (3) insufisiensi adrenal tersier, bila disebabkan oleh penyakit hipotalamus.⁸ Terminologi untuk insufisiensi adrenal yang diinduksi oleh glukokortikoid disebut insufisiensi adrenal iatrogenik, sekunder, atau tersier.⁴

Pengobatan dengan glukokortikoid dapat menyebabkan insufisiensi adrenal melalui supresi umpan balik (*feedback mechanism*) *corticotropin-releasing hormone* (CRH) dan ACTH. Pada akhirnya, kondisi ini menginduksi hipoplasia dan atrofi adrenokortikal, serta membuat aksis HPA tidak dapat menghasilkan respons kortisol yang memadai terhadap stres. Insufisiensi adrenal dapat bertahan setelah penghentian pengobatan glukokortikoid. Insufisiensi adrenal primer dan insufisiensi adrenal sekunder karena gangguan struktural jarang terjadi, dengan prevalensi 100–200 per satu juta orang. Namun, kedua kondisi tersebut tergolong serius dan memerlukan diagnosis segera dan terapi penggantian hormon yang dapat menyelamatkan nyawa penderitanya.⁸ Sebaliknya, insufisiensi adrenal yang diinduksi glukokortikoid dilaporkan jauh lebih umum terjadi, meskipun implikasi klinisnya kurang jelas.^{9–11}

Setelah diabsorpsi, glukokortikoid akan memasuki sirkulasi sistemik melalui metabolisme lintas pertama dan memicu respons umpan balik negatif terhadap aksis HPA dengan menurunkan sintesis dan sekresi *corticotropin releasing hormone* (CRH) dan menghambat pelepasan ACTH oleh hipofisis anterior. Efek akut glukokortikoid pada hipofisis adalah menekan sintesis *proopiomelanocortin* (POMC), hormon ACTH, serta turunan peptida POMC lainnya. Dalam jangka panjang, kondisi ini dapat menyebabkan terjadinya atrofi sel kortikotrof dan sel *Crooke*. Perubahan sel *Crooke* dapat ditemukan pada sindrom *Cushing* endogen maupun iatrogenik, yang ditandai dengan cincin hialin intrasitoplasma (filamen keratin), vakuola paranuklear (lisosom), dan butiran sekretori. Dengan tidak adanya ACTH, korteks adrenal kehilangan kemampuan untuk memproduksi kortisol dan androgen sehingga akhirnya mengalami atrofi. Sekresi aldosteron tetap dipertahankan.¹²

Gambar 4. menjelaskan representasi skematis pemulihan aksis HPA setelah penghentian terapi glukokortikoid. Setelah pengobatan jangka pendek dengan glukokortikoid, sekresi ACTH yang pertama mengalami pemulihan, diikuti CRH lalu kortisol dan androgen. Setelah paparan jangka panjang, akan terjadi peningkatan ACTH yang cepat dan nyata. Hal ini mendahului pemulihan sekresi kortisol.¹² Sekresi kortisol yang abnormal dapat berlangsung sangat lama jika atrofi adrenal telah terjadi. Produksi androgen adrenal juga tetap dapat ditekan dalam jangka panjang. Dosis harian *prednisolone* 5 mg atau lebih pada orang dewasa, serta setara dengan 10–15 mg/m² atau lebih pada anak-anak, dapat mengakibatkan supresi aksis HPA jika diberikan selama 1 bulan atau lebih secara oral, inhalasi, intranasal, intraartikular, maupun topikal. Pemberian glukokortikoid kronis merupakan penyebab paling umum dari supresi adrenal sekunder, yang dapat pula disebut sebagai insufisiensi adrenal tersier.⁵

Kasus ini mempresentasikan seorang pasien yang mengonsumsi steroid jangka panjang sejak kurang lebih 5 tahun sebelum masuk rumah sakit, dan semakin rutin sejak 6 bulan sebelum masuk rumah sakit. Hal ini menunjukkan penggunaan jangka panjang steroid melebihi satu bulan tanpa pengawasan tenaga kesehatan. Steroid yang dikonsumsi dalam jangka panjang tersebut mengganggu mekanisme umpan balik negatif aksis HPA sehingga terjadi insufisiensi adrenal tersier. Kondisi ini ditunjukkan secara signifikan melalui manifestasi klinis pasien, antara lain wajah *moon face*, alopesia, penurunan berat badan, gejala gastrointestinal (nyeri ulu hati, mual, diare), kelemahan kronis, serta gejala yang berkaitan dengan kondisi imunodefisiensi sekunder akibat penggunaan steroid yang menyebabkan pasien rentan mengalami infeksi sekunder.

Manifestasi Klinis

Insufisiensi adrenal tersier akibat pengobatan steroid secara paradoks memiliki gambaran *cushingoid*.³ Gejala klinis insufisiensi adrenal bergantung pada kecepatan dan tingkat kerusakan adrenal, yang biasanya ditemukan pada usia pertengahan. Penyakit ini berlangsung selama beberapa bulan hingga bertahun-tahun dengan keluhan tidak spesifik, seperti lesu, letih, lemah, anoreksia, mual dan penurunan berat badan. Keluhan lain dapat berupa muntah dan nyeri perut. Pada pemeriksaan fisik dan lanjutan, pasien terlihat kurus, mengalami kelemahan kronis, hipoglikemia, dan hipotensi postural.⁷ Semua gejala klinis tersebut di atas ditemukan pada pasien dalam laporan kasus ini.

Hipotensi yang resistan terhadap pemberian cairan merupakan tanda kardinal insufisiensi adrenal akut, tetapi hal ini sudah merupakan tanda agonal.⁵ Sebelum terjadi syok hipovolemik, sangat penting untuk mewaspadaai gejala dan tanda awal, antara lain:

1. Malaise nonspesifik; mengantuk atau tingkat kesadaran menurun disertai disfungsi kognitif. Respons terhadap pemberian *hydrocortisone* intravena 100 mg dapat diuji.
2. Hipotensi ortostatik.
3. Hiponatremia, peningkatan protein C-reaktif (tes ini memiliki nilai terbatas pada periode pascaoperasi).
4. Pireksia persisten yang mungkin disebabkan oleh insufisiensi adrenal, tetapi biasanya dikaitkan dengan sepsis pascaoperasi dan diobati dengan antibiotik. Suplementasi steroid tidak boleh dikurangi atau dihentikan saat pasien demam.⁵

Pasien yang dilaporkan pada kasus ini menunjukkan kondisi kelemahan kronis nonspesifik, syok hipovolemik (telah membaik), dan hiponatremia ringan. Menjaga keseimbangan cairan perioperatif sangat penting, sehingga retensi natrium dan air akibat suplementasi perlu diperhatikan. Kontrol glikemik dianggap penting pada pasien diabetes, dan glikemia yang diinduksi glukokortikoid dapat terjadi, meskipun biasanya dapat dikontrol dengan mudah. Potensi efek negatif glukokortikoid terhadap penyembuhan luka, peningkatan risiko infeksi, serta ulserasi peptik menjadi perhatian lebih lanjut.⁵ Pasien pada kasus ini sempat mengalami hipoglikemia saat dirawat, serta adanya keluhan nyeri ulu hati dan riwayat hematemesis saat dirawat di rumah sakit sebelumnya.

Implikasi klinis insufisiensi adrenal yang diinduksi glukokortikoid memiliki karakteristik yang buruk.^{5,13} Krisis adrenal dapat terjadi sebagai akibat stres, bahkan tidak jarang pasien mengalami depresi dan psikosis.⁷ Pasien dengan penyakit komorbid lebih rentan terhadap krisis adrenal, terutama mereka yang menderita asma dan diabetes. Pasien dengan ketergantungan mineralokortikoid atau vasopresin juga biasanya datang dengan kondisi kurang stabil dibandingkan pasien dengan insufisiensi adrenal sekunder yang masih memiliki fungsi mineralokortikoid intact.⁵

Komplikasi

Pasien dengan insufisiensi adrenal akibat penggunaan steroid yang tidak tepat dapat mengalami komplikasi hingga kematian akibat krisis adrenal, yang seharusnya dapat dicegah sepenuhnya. Banyak pasien yang mengalami krisis adrenal sebelum diagnosis insufisiensi adrenal tersebut ditegakkan.⁵ Krisis adrenal atau insufisiensi adrenokortikal akut merupakan defisiensi kortisol absolut atau relatif yang terjadi secara spontan. Kondisi ini biasanya dipicu oleh suatu penyakit atau stres berat, yang menyebabkan respons adrenal menurun atau terjadi gangguan pelepasan ACTH akibat kerusakan hipofisis maupun terapi kortikosteroid. Penggunaan steroid secara luas menjadi salah satu penyebab insufisiensi adrenal yang sering terjadi.⁷ Pengenalan dini terhadap tanda dan gejala klinis insufisiensi adrenal sangat penting agar tata laksana yang tepat dapat segera diberikan sebelum berkembang menjadi krisis adrenal.⁵ Laporan kasus ini menunjukkan kondisi gejala klinis insufisiensi adrenal yang telah berlangsung lama, namun pasien dibawa ke UGD sudah dalam kondisi krisis adrenal yang ditandai dengan hipotensi, hipoglikemia, serta gejala gastrointestinal (mual, nyeri ulu hati). Krisis adrenal ini kemungkinan dicetuskan oleh faktor stres akut, yang dalam kasus ini berupa infeksi sekunder pada *tophus* multipel yang diderita pasien. Meski penegakkan diagnosis masih belum dapat dilakukan karena keterbatasan sumber daya, penanganan awal terhadap kondisi saat pasien datang ke UGD sudah diberikan.

Dosis dan durasi terapi steroid merupakan faktor risiko independen dari dampak negatif penggunaan jangka panjang. Dosis suprafisiologis kortikosteroid dapat menyebabkan supresi ringan aksis HPA hingga infeksi berat yang mengancam jiwa. Namun, penggunaan glukokortikoid dosis rendah hingga sedang dalam jangka panjang juga dapat menimbulkan efek samping yang serius.^{2,14}

Sebuah kohort terhadap 1.675 pasien di Swedia dengan insufisiensi adrenal menunjukkan rasio risiko untuk semua penyebab kematian adalah 2,19 untuk pria dan 2,86 untuk wanita. Krisis adrenal yang membutuhkan perawatan di rumah sakit terjadi sekitar 6–8 kali per 100 pasien per tahun di antara populasi pasien dengan insufisiensi adrenal primer atau sekunder akibat penyakit adrenal dan gangguan hipotalamus-hipofisis.⁵ Selain itu, sebuah survei di Inggris menunjukkan 8,6% pasien dengan insufisiensi adrenal kronis melaporkan pernah mengalami krisis adrenal sebelumnya akibat dosis glukokortikoid yang tidak adekuat selama rawat inap, misalnya saat menjalani operasi elektif.¹⁵ Komplikasi berupa krisis adrenal pada kondisi insufisiensi adrenal ini juga dikonfirmasi oleh studi prospektif lainnya, yang menunjukkan bahwa hal tersebut dapat berulang pada periode rawat inap selanjutnya.^{16,17}

Penggunaan glukokortikoid dosis sedang hingga tinggi dapat menimbulkan komplikasi berupa kondisi *immunocompromised* yang meningkatkan risiko infeksi secara signifikan, termasuk infeksi ringan yang umum maupun infeksi serius yang

mengancam jiwa.⁶ Pada kasus ini, pasien ditemukan dengan klinis *immunocompromised* yang tidak dapat dijelaskan dengan kondisi imunodefisiensi sekunder lainnya. Oleh karena itu, riwayat penggunaan steroid jangka panjang serta gambaran klinis sindrom *Cushing* mengarahkan pada kemungkinan insufisiensi adrenal tersier. Risiko infeksi meningkat secara linier seiring dengan dosis dan durasi terapi, terutama terhadap infeksi bakteri, virus, dan jamur yang umum.¹⁸ Dosis *prednisone* kurang dari 10 mg per hari umumnya menimbulkan risiko infeksi yang minimal atau bahkan tidak ada sama sekali. Pasien yang menggunakan glukokortikoid sering kali tidak menunjukkan tanda dan gejala infeksi secara jelas. Hal ini terjadi karena steroid menghambat pelepasan sitokin serta menurunkan respons inflamasi dan demam, sehingga menyebabkan kegagalan pengenalan infeksi secara dini.⁶

Tata Laksana

Tata laksana insufisiensi adrenal saat ini tidak bersifat kuratif, melainkan hanya menggantikan konsentrasi kortisol fisiologis. Hal ini menjadi tantangan tersendiri mengingat adanya variasi fisiologis sirkadian dan ultradian dalam konsentrasi kortisol. Pengobatan jangka panjang ditujukan untuk menghentikan proses destruksi oleh mekanisme autoimun. Sekitar 15–30% pasien masih dapat memproduksi kortikosteroid, bahkan bertahun-tahun setelah diagnosis ditegakkan.¹⁹

Pedoman penanganan insufisiensi adrenal oleh Woodcock dkk. menekankan bahwa tujuan terapi adalah memastikan pasien dengan kondisi ini dapat diidentifikasi dan diberikan suplemen glukokortikoid secara adekuat.⁵ Pasien yang menggunakan kortikosteroid dosis pengganti fisiologis untuk insufisiensi adrenal primer atau sekunder memiliki risiko krisis adrenal yang signifikan dan harus diberikan dosis stres *hydrocortisone* pada kondisi tertentu, misalnya selama periode perioperatif.

Selain pasien dengan kegagalan adrenal primer atau sekunder (gangguan pada hipotalamus-hipofisis), banyak pula pasien yang menerima glukokortikoid sebagai pengobatan untuk kondisi medis lainnya. Pendekatan pragmatis diperlukan untuk penggantian adrenal selama stres berat; dosis substitusi adrenal setelah stress pembedahan atau penyakit berat merupakan tambahan dari pengobatan steroid yang biasa digunakan pasien. Pasien dengan insufisiensi adrenal yang sebelumnya tidak terdiagnosis dapat ditemukan dengan kondisi insufisiensi adrenal pertama kalinya setelah stres pascapembedahan. Suplementasi yang tidak adekuat atau insufisiensi adrenal yang tidak terdiagnosis harus segera dideteksi dan diobati, karena penundaan penanganan dapat berakibat fatal.⁵

Pasien pada kasus ini telah mendapatkan terapi steroid berupa *methylprednisolone* 62,5 mg intravena setiap 24 jam selama tiga hari untuk mengatasi kondisi stres akut, yang kemudian dilanjutkan dengan pemberian oral 16 mg setiap 12 jam. Meski bukan merupakan steroid standar untuk substitusi kortisol, *methylprednisolone* tetap dapat digunakan.²⁰ Terapi penggantian secara fisiologis harus dipastikan berjalan dengan baik, dan dosis harian harus ditingkatkan pada saat terjadi stres fisiologis. Dosis yang direkomendasikan adalah *hydrocortisone* intravena 100 mg, dilanjutkan dengan infus 200 mg setiap 24 jam. Pemulihan dapat dicapai dengan menggandakan dosis substitusi (*replacement*) *hydrocortisone* oral reguler selama 48 jam hingga seminggu setelah stres berat sebelum kembali ke dosis pemeliharaan (misalnya, jika dosis substitusi harian biasanya adalah 10-5-5 mg *hydrocortisone*, dosis digandakan menjadi 20-10-10 mg selama seminggu setelah kondisi stres berat, dengan asumsi pasien pulih dengan baik). Namun, jika kondisi klinis pasien tidak kunjung membaik atau pasien menjadi kritis, maka pemberian dosis stres dengan infus intravena kontinu harus dilanjutkan.⁵

Pembelajaran Klinis dari Kasus

Glukokortikoid memberikan efek umpan balik negatif pada aksis HPA, yang secara langsung menekan sekresi ACTH dan CRH. Selain itu, dengan menekan pelepasan sitokin proinflamasi yang merangsang sekresi ACTH dan CRP, glukokortikoid juga menekan sekresi ACTH dan CRH secara tidak langsung pada penyakit inflamasi. Supresi aksis HPA kronis oleh glukokortikoid menyebabkan atrofi adrenal fungsional. Risiko atrofi dan insufisiensi adrenal fungsional ini sulit diprediksi,

bervariasi antar pasien, dan sebagian besar bergantung pada dosis serta durasi terapi glukokortikoid.^{21,22}

Observasi fungsi aksis HPA harus diperketat jika pasien telah menerima kortikosteroid sistemik selama lebih dari dua minggu berturut-turut atau lebih dari tiga minggu kumulatif dalam enam bulan terakhir, atau jika pasien memiliki gejala supresi adrenal yang persisten. Skrining awal dapat dilakukan dengan mengukur kadar kortisol pagi hari. Jika kadar kortisol pagi hari normal tetapi pasien memiliki gejala supresi adrenal, uji stimulasi ACTH dosis rendah dapat dilakukan untuk memastikan diagnosis. Rujukan ke spesialis endokrinologi untuk mengonfirmasi diagnosis dapat dipertimbangkan.⁶

Kesimpulan

Kasus ini melaporkan seorang pria usia produktif dengan penyakit dasar *gout arthritis* dan kecurigaan insufisiensi adrenal dengan gambaran klinis krisis adrenal saat datang ke unit gawat darurat. Pasien juga menunjukkan tanda imunodefisiensi sekunder serta gambaran *cushingoid*. Pasien diketahui memiliki riwayat penggunaan steroid jangka panjang tanpa pengawasan tenaga kesehatan. Meskipun penegakkan diagnosis melalui pemeriksaan kortisol plasma baru dapat mengonfirmasi kecurigaan tersebut saat pasien menjalani perawatan di poliklinik, tata laksana yang diperlukan telah diberikan pada pasien dengan adekuat.

Penerapan teknik anamnesis yang strategis dan pengenalan dini terhadap kondisi klinis yang signifikan, seperti kondisi gangguan adrenal akibat steroid, merupakan kompetensi yang harus didalami oleh dokter spesialis penyakit dalam. Hal ini krusial mengingat permasalahan penggunaan steroid jangka panjang tanpa pengawasan tenaga kesehatan sering ditemukan pada masyarakat dan belum diimbangi dengan strategi skrining yang adekuat. Tata laksana awal untuk kondisi akut sangat menentukan luaran klinis pasien, meskipun penegakkan diagnosis baru dapat dilakukan kemudian.

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Physiologically Based Pharmacokinetic (PBPK) Simulation of Supratherapeutic Meropenem Exposure and Potential Pharmacokinetics/Pharmacodynamics (PK/PD) Discordance in a Critically Ill Pediatric Patient: A Case Report

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Abstract

Background: Meropenem is widely used in critically ill pediatric patients; however, sepsis and renal impairment can markedly alter its pharmacokinetics profile, increasing the risk of drug accumulation. Furthermore, therapeutic drug monitoring is not readily available in many clinical settings. **Case presentation:** A 6-year-old child (body weight 18.6 kg, height 102 cm) presented with severe pneumonia and sepsis complicated by acute kidney injury. Laboratory findings showed elevated serum creatinine (1.9 mg/dl), reduced estimated glomerular filtration rate (eGFR) (22.17 ml/minute/1.73 m²), mild hypoalbuminemia (3.2 g/dl), and elevated transaminase levels (AST 67 U/l, ALT 89 U/l). Intravenous meropenem was administered, and a physiologically based pharmacokinetic (PBPK) model was utilized to assess and predict drug exposure. **Methods:** PBPK simulations were performed using PK-Sim®, incorporating pediatric physiology, impaired renal clearance, low protein binding, and drug-specific physicochemical properties. **Results:** The model predicted marked meropenem accumulation following repeated dosing. The predicted plasma concentration at 0.5 hours postdose ($C_{0.5}$) was 69.82 mcg/ml. After the fourth dose, the predicted peak concentration (C_{max}) reached 183.42 mcg/ml, while the trough concentration (C_{trough}) remained elevated at 139.94 mcg/ml. Free drug concentrations remained above the minimum inhibitory concentration (MIC) throughout the dosing interval, resulting in 100% fT>MIC. Supratherapeutic concentrations caused by altered PK/PD may lead to neurotoxicity in critically ill children, whereas even therapeutic dosing may result in microbiome alterations. **Conclusion:** This case demonstrates that standard meropenem dosing in critically ill pediatric patients with renal impairment may lead to supratherapeutic exposure despite full pharmacodynamic target attainment. PBPK modeling may help anticipate exposure extremes and support individualized dosing when renal function is unstable and therapeutic drug monitoring is unavailable.

Keywords: PBPK, meropenem, pharmacokinetics

Abstrak

Latar belakang: Meropenem digunakan secara luas pada pasien anak dengan kondisi kritis; namun, sepsis dan gangguan fungsi ginjal dapat mengubah profil farmakokinetika secara bermakna, sehingga meningkatkan risiko akumulasi obat. Lebih lanjut, pemantauan kadar obat terapeutik belum tersedia secara memadai di banyak fasilitas kesehatan. **Presentasi kasus:** Seorang anak berusia 6 tahun (berat badan 18,6 kg, tinggi badan 102 cm) datang dengan pneumonia berat dan sepsis yang disertai gangguan ginjal akut. Pemeriksaan laboratorium menunjukkan peningkatan kreatinin serum (1,9 mg/dl), penurunan estimasi laju filtrasi glomerulus (eLFG) (22,17 ml/menit/1,73 m²), hypoalbuminemia ringan (3,2 g/dl), serta peningkatan

kadar transaminase (AST 67 U/l, ALT 89 U/l). Pasien mendapatkan *meropenem* intravena, dan model farmakokinetika berbasis fisiologi (*physiologically based pharmacokinetic/PBPK*) digunakan untuk menilai dan memprediksi paparan obat. **Metode:** Simulasi PBPK dilakukan menggunakan PK-Sim®, dengan mempertimbangkan fisiologi anak, gangguan klirens ginjal, ikatan protein yang rendah, serta sifat fisikokimia spesifik obat. **Hasil:** Model memprediksi adanya akumulasi *meropenem* yang bermakna setelah pemberian dosis berulang. Konsentrasi plasma yang diprediksi pada 0,5 jam setelah pemberian dosis ($C_{0,5}$) adalah 69,82 mcg/ml. Setelah dosis keempat, prediksi konsentrasi puncak (C_{maks}) mencapai 183,42 mcg/ml, sementara konsentrasi *trough* (C_{trough}) tetap tinggi pada 139,94 mcg/ml. Konsentrasi obat bebas tetap berada di atas kadar hambat minimum (*minimum inhibitory concentration/MIC*) sepanjang interval dosis, menghasilkan $ft > MIC$ sebesar 100%. Konsentrasi supratherapeutik akibat perubahan PK/PD dapat menyebabkan neurotoksisitas pada pasien anak dengan kondisi kritis; bahkan pada dosis terapeutik *meropenem* dapat menyebabkan perubahan pada mikrobiom. **Kesimpulan:** Kasus ini menunjukkan bahwa pemberian dosis standar *meropenem* pada pasien anak dengan kondisi kritis disertai gangguan fungsi ginjal dapat menyebabkan paparan supratherapeutik, meskipun target farmakodinamika telah tercapai sepenuhnya. Pemodelan PBPK dapat membantu mengantisipasi paparan yang berlebihan dan mendukung penyesuaian dosis secara individual ketika fungsi ginjal tidak stabil dan pemantauan kadar obat terapeutik tidak tersedia.

Kata kunci: PBPK, *meropenem*, farmakokinetika

Introduction

Critically ill pediatric patients often experience profound and dynamic physiological alterations that significantly affect drug pharmacokinetics (PK) and pharmacodynamics (PD). Clinical conditions such as sepsis, severe pneumonia, hypoalbuminemia, and impaired renal function can disrupt multiple pharmacokinetic processes, including absorption, distribution, metabolism, and excretion. These pathophysiological changes are frequently unpredictable and may vary over the course of illness, making standard dosing regimens difficult to apply safely and effectively. Consequently, these conditions may lead to substantial interpatient variability in drug concentrations, potentially resulting in subtherapeutic exposure, particularly during the early phase of treatment. Conversely, as organ dysfunction progresses, drug clearance may be markedly reduced, leading to drug accumulation and supratherapeutic plasma concentrations.^{1,2}

Meropenem is a broad-spectrum β -lactam antibiotic commonly used to treat severe infections in intensive care settings. It belongs to the carbapenem class, a group of reserve antibiotics with potent activity against a wide range of gram-negative, gram-positive, and anaerobic pathogens, including multidrug-resistant organisms such as extended-spectrum β -lactamase (ESBL)-producing Enterobacterales. Because of this broad spectrum and high efficacy, meropenem is frequently selected as a last-line or escalation therapy for life-threatening infections, including sepsis, severe pneumonia, and intra-abdominal infections, particularly in critically ill pediatric and adult patients.^{3–5} The pharmacodynamic activity of meropenem is best described by the time-dependent parameter $ft > MIC$, where free drug concentrations must remain above the minimum inhibitory concentration (MIC) for at least 40–70% of the dosing interval to achieve optimal clinical outcomes. However, standard dosing regimens may be inadequate in children with altered physiology due to critical illness.⁶

Physiologically based pharmacokinetic (PBPK) modeling is increasingly recognized as a promising tool for predicting drug exposure in critically ill patients, particularly in settings where therapeutic drug monitoring (TDM) is unavailable, delayed, or impractical.^{7,8} PBPK models integrate drug-specific physicochemical properties with patient-specific physiological parameters such as organ function, age, body composition, and disease-related changes, to mechanistically simulate drug absorption, distribution, metabolism, and excretion (ADME).⁹

In critically ill pediatric patients, conventional dosing strategies are often insufficient due to profound and rapidly evolving physiological alterations, including sepsis-related inflammation, fluid shifts, hypoalbuminemia, and fluctuating renal

function. These factors lead to high inter- and intra-individual variability in drug concentrations, making it difficult to predict systemic exposure using standard population-based approaches alone. While TDM remains the gold standard for measuring actual drug concentrations, it is not always feasible due to logistical constraints, limited assay availability, small blood volumes in children, or delayed turnaround times.^{9,10}

This case report presents a PBPK simulation of a pediatric patient with a clinical diagnosis of pneumonia and sepsis, aiming to characterize meropenem pharmacokinetics in the setting of critical illness and organ dysfunction, and to evaluate whether the current dosing regimen achieves adequate pharmacodynamic target attainment. The simulation further explores the potential implications of supratherapeutic meropenem exposure, including PK/PD discordance and theoretical risks related to neurotoxicity and microbiome disruption. The clinical importance of this case lies not in a rare diagnosis, but in an under-recognized yet clinically common scenario in which standard weight-based meropenem dosing in a critically ill child with unstable renal function may potentially result in harm, particularly in settings where TDM is unavailable. This case illustrates how a routine dosing decision can lead to markedly supratherapeutic drug exposure that may remain clinically unrecognized because the conventional pharmacodynamic target ($fT > MIC$) is fully achieved. Furthermore, it demonstrates how PBPK modeling can help reveal this hidden overexposure at the bedside. Importantly, this learning point is directly applicable to everyday pediatric intensive care practice.

Case Presentation

A 6-year-old girl weighing 18.6 kg with a height of 102 cm was admitted to the pediatric ward with a diagnosis of severe community-acquired pneumonia. She presented with a one-week history of high-grade fever, productive cough, with worsening shortness of breath over the preceding three days. The sputum was thick, yellow-colored, and difficult to expectorate. The fever had persisted despite antipyretic treatment. Prior to admission, the patient had been treated with azithromycin 200 mg once daily for three days at a primary care facility. However, she showed no clinical improvement, prompting referral to a higher-level care facility.

On admission, the patient appeared mildly somnolent but was responsive to verbal stimuli. Vital signs indicated systemic infection, with fever (38.7°C), tachypnea (30 breaths/minute), and tachycardia (119 beats/minute). Nutritional assessment revealed a body mass index (BMI) of 17.9 kg/m², which was within the normal range for age. The clinical presentation was consistent with severe pneumonia complicated by sepsis, prompting the initiation of intravenous (IV) meropenem therapy and close monitoring in the pediatric intensive care unit (PICU).

Initial laboratory investigations revealed a hemoglobin concentration of 11.6 g/dl; white blood cell count of 17,596/mcl (87% neutrophils); platelet count of 325,300/mcl; serum creatinine of 1.9 mg/dl; AST (SGOT) of 67 U/l, ALT (SGPT) of 89 U/l; serum sodium (Na) of 127 mmol/l, potassium (K) of 4.1 mmol/l, and chloride (Cl) of 98 mmol/l; urine specific gravity of 1.005 with no proteinuria or hematuria; and serum albumin of 3.2 g/dl. The clinical and laboratory findings were consistent with severe bacterial pneumonia accompanied by systemic inflammatory response, renal impairment, and hyponatremia. Given the lack of response to azithromycin and the severity of illness, the patient was started on empiric meropenem 400 mg IV every 8 hours, infused over 30 minutes.

Methods

PBPK Model Constructions

A physiologically based pharmacokinetic (PBPK) model was developed using PK-Sim® version 12, part of the Open Systems Pharmacology Suite. The model was developed to predict plasma and lung tissue concentrations of meropenem in a pediatric patient with altered physiology due to sepsis and renal impairment. The virtual patient profile was generated based on clinical data obtained at admission, as summarized in **Table 1**.

Table 1. Patient clinical data used for virtual patient construction in PK-Sim®

Clinical parameter	Values
Age	6 years
Body weight	18.6 kg
Height	102 cm
Serum creatinine	1.9 mg/dl
Estimated glomerular-filtration rate (eGFR)	22.17 ml/minute/1.73 m ²
Serum albumin	3.2 g/dl
AST	67 U/l
ALT	89 U/l

Meropenem Drug Compound

The physicochemical and pharmacokinetics (absorption, distribution, metabolism, and excretion/ADME) parameters of meropenem are presented in **Table 2**. Relevant and appropriate algorithms were selected from the available options in PK-Sim® to construct a PBPK model for pediatric patients with sepsis receiving intravenous meropenem, following the guidance-based workflow provided by the software.

Table 2. Physicochemical and pharmacokinetics parameters of meropenem used for PBPK model^{11–14}

Drug data	Values
Molecular weight	383.5 g/mol
Lipophilicity (LogP)	-1.39
Fraction unbound (fu)	0.98
Solubility	5.63 mg/ml
pH references	7.0
Protein binding	Albumin
pKa base	3.47
pKa acid	7.4
Distribution model	Rodgers–Rowland
Cellular permeability model	PK-Sim standard
Renal clearance (CL _{renal})	3.34±1.19 ml/minute/kg

Validation

Internal validation was performed using the conventional pharmacokinetic equation for initial plasma concentration (C₀). The objective was to verify that the simulated peak concentration (C_{max}) aligned with the expected theoretical value, calculated based on the administered dose and volume of distribution (Vd). This comparison was intended to confirm the physiological plausibility of the model and its consistency with fundamental pharmacokinetic principles. The volume of distribution (Vd) was derived from previously published pharmacokinetic studies.^{12–14}

Results

The PBPK model outputs are summarized in **Figure 1** and **Table 3**. The simulation demonstrated progressive accumulation of meropenem following repeated dosing in a critically ill pediatric patient with sepsis and acute kidney injury (AKI). Predicted plasma concentrations increased with each successive dose, reflecting reduced drug elimination associated with impaired renal function. After the fourth dose (at which point predicted concentrations had effectively reached the simulated steady state, with negligible further increase across subsequent dosing intervals shown in **Figure 1**), the predicted plasma concentration at 0.5 hours postdose (C_{0.5}) was 69.82 mcg/ml, the predicted peak concentration (C_{max}) reached 183.42 mcg/ml, and the trough concentration (C_{trough}) remained elevated at 139.94 mcg/ml. Free drug concentrations remained above the minimum inhibitory concentration throughout the dosing interval, resulting in 100% ft>MIC. Pharmacodynamic target

attainment was evaluated using $fT>MIC$ based on microbiological susceptibility results obtained during hospitalization ($MIC\ 2\ mcg/ml$). These findings indicate complete pharmacodynamic target attainment (PTA) despite substantial drug accumulation. This outcome highlights a discordance between conventional PK/PD target achievement and excessive systemic exposure, which may increase the risk of concentration-related neurotoxicity and microbiome disruption.

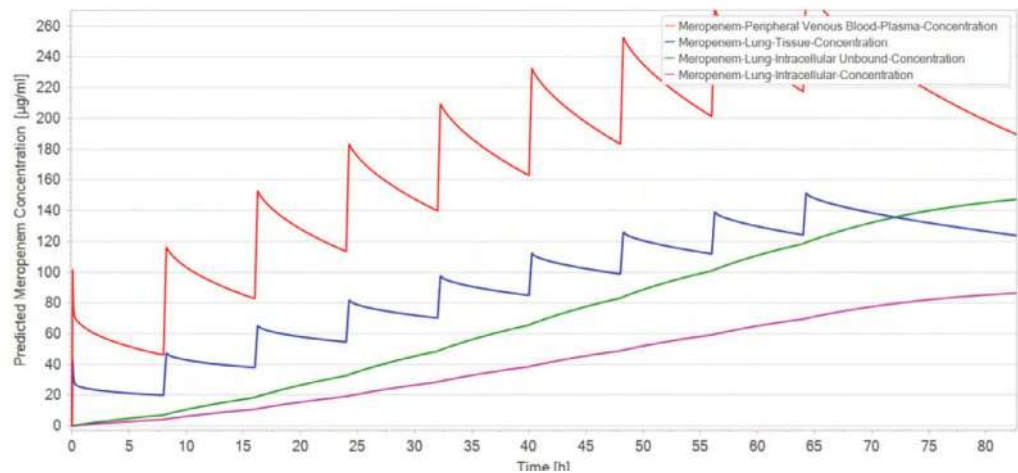


Figure 1. PBPK-simulated meropenem concentration–time profiles in peripheral venous blood plasma and lung compartments following repeated intravenous administration of meropenem (400 mg every 8 hours) in a 6-year-old pediatric patient with sepsis and acute kidney injury

Table 3. Predicted meropenem pharmacokinetic parameters derived from PBPK simulation

Parameter	Predicted meropenem concentration
$C_{0.5}$	69.82 mcg/ml
C_{max} (4 th dose)	183.42 mcg/ml
C_{trough} (4 th dose)	139.94 mcg/ml
$fT>MIC$	100%
Clearance (Cl)	0,8 l/hour

Abbreviations: $C_{0.5}$: plasma concentration at 0.5 hours postdose; C_{max} : peak plasma concentration; C_{trough} : trough plasma concentration; $fT>MIC$: fraction of dosing interval during which free drug concentration exceeds the minimum inhibitory concentration

Discussion

The main finding of this case is that standard weight-based meropenem dosing (400 mg every 8 hours) in a critically ill child with acute kidney injury produced markedly supratherapeutic predicted exposure ($C_{max}\ 183.42\ mcg/ml$; $C_{trough}\ 139.94\ mcg/ml$) while simultaneously achieving 100% $fT>MIC$. In other words, full pharmacodynamic target attainment coexisted with exposure well above conventional safety thresholds, illustrating a clinically silent PK/PD discordance that would not have been detected without modeling, given the absence of therapeutic drug monitoring. The remainder of the discussion examines the pharmacokinetic basis for this accumulation and its potential safety and ecological implications.

Supratherapeutic drug concentrations are often unrecognized in healthcare settings where TDM is unavailable. This is particularly important for drugs with a narrow therapeutic index and concentration-dependent adverse effects. Such clinically silent overexposure may evolve into drug-related clinical manifestations that are misinterpreted as part of the underlying disease progression or its complications, leading clinicians to overlook the contribution of excessive drug exposure.

PBPK and Pharmacokinetic Alteration

The PBPK simulation demonstrated progressive accumulation of meropenem following repeated intermittent infusion dosing (400 mg every 8 hours) in a pediatric patient with severe renal impairment (eGFR 22 ml/minute/1.73 m²). The predicted C_{max} reached 183.42 mcg/ml, while C_{trough} remained markedly elevated at 139.94 mcg/ml, resulting in 100% fT>MIC. These findings are consistent with substantial meropenem accumulation in the setting of acute kidney injury. Persistently elevated meropenem exposure has been associated with an increased risk of toxicity, particularly neurotoxicity such as seizures and encephalopathy.¹⁵ Clearance was markedly reduced (0.8 l/hour) and the half-life prolonged, consistent with clinical expectations in acute kidney injury.

Previous studies have reported that meropenem pharmacokinetics are highly dependent on renal function; therefore, reduced eGFR may lead to significant drug accumulation, as observed in this simulation. Supratherapeutic C_{max} values (>100 mcg/ml) and persistently elevated C_{trough} have been associated with an increased risk of toxicity, particularly neurotoxicity including seizures or encephalopathy.^{15,16} This reflects real-world clinical challenges, wherein imprecise estimation of renal function or rapidly evolving renal dysfunction may result in inadvertent overdosing if dose adjustments are not performed accordingly.^{6,17}

The PBPK simulation results in this case were consistent with published population pharmacokinetic data demonstrating that renal function is the primary determinant of meropenem clearance in critically ill patients. A recent prospective population PK study reported a median meropenem clearance of 13.7 l/hour in patients with preserved or augmented renal function, underscoring the strong dependence of meropenem elimination on glomerular filtration rate. Consequently, in patients with impaired renal function, substantial reductions in clearance and pronounced drug accumulation are anticipated, leading to elevated C_{max} and persistently high C_{trough} concentrations. Such exposure profiles may ensure sustained fT>MIC target attainment while simultaneously increasing the risk of excessive systemic exposure and potential toxicity, supporting the findings observed in the present PBPK simulation.^{13,18}

In critically ill patients, pharmacokinetic alterations are commonly observed due to underlying organ dysfunction. In the setting of renal impairment, particularly acute kidney injury (AKI), a reduction in glomerular filtration rate leads to impaired elimination of drugs that are predominantly excreted unchanged in the urine. Consequently, systemic clearance is significantly reduced and the elimination half-life is prolonged, resulting in drug accumulation following repeated dosing, as reflected by increased C_{max} and C_{trough} concentrations. In addition, AKI is associated with other physiological changes, such as reduced renal blood flow and altered tubular transporter function, which further impair drug excretion. In pediatric patients, these effects are further compounded by developmental renal immaturity and markedly interindividual variability, making pharmacokinetic responses more difficult to predict. Therefore, without appropriate dose adjustment, renally eliminated drugs carry an increased risk of accumulation and toxicity.^{18–21}

These alterations are further exacerbated in the presence of sepsis, which induces profound physiological disturbances that markedly affect drug pharmacokinetics. The systemic inflammatory response increases capillary permeability and promotes fluid redistribution from the intravascular to the extravascular compartment, leading to an increased volume of distribution (Vd), particularly for hydrophilic antibiotics such as meropenem.^{21,22} This expansion of Vd may result in lower

than expected or unpredictable initial plasma concentrations. Sepsis is also frequently associated with hemodynamic changes, including vasodilation and impaired organ perfusion, which can influence both drug distribution and elimination.²⁰ During the early phase of sepsis, some patients may exhibit augmented renal clearance (ARC), whereas in later stages or in the setting of severe sepsis, AKI commonly develops. These rapid and dynamic fluctuations in renal function result in highly variable drug clearance over time. Moreover, multiorgan dysfunction and altered plasma protein binding during sepsis can increase the unbound drug fraction, directly influencing pharmacodynamic activity and the potential for toxicity. The combination of increased Vd, altered clearance, and rapidly evolving disease dynamics makes pharmacokinetic prediction in septic patients particularly challenging.^{13,18,23,24}

Medicinal Chemistry of Meropenem in Critically Ill Patients

Changes in the pharmacokinetics of meropenem are also supported by its physicochemical properties. Medicinal chemistry studies have demonstrated that the pharmacokinetic behavior of meropenem is largely governed by its intrinsic physicochemical characteristics. Meropenem is a carbapenem-class beta-lactam antibiotic that is highly hydrophilic, has a relatively low molecular weight (383.5 Da), exhibits low plasma protein binding (fraction unbound 0.98), and undergoes minimal hepatic metabolism.¹¹ The combination of these properties renders meropenem elimination almost exclusively dependent on renal function.

From a medicinal chemistry standpoint, meropenem possesses a highly polar chemical structure with multiple charged functional groups, conferring excellent aqueous solubility but limited penetration into lipophilic tissues. Under normal physiological conditions, these properties result in a relatively small volume of distribution and relatively predictable plasma concentration profiles. In the setting of sepsis, pathophysiological changes such as increased capillary permeability and expansion of the extracellular fluid compartment, substantially alter drug distribution. As a result, the volume of distribution of hydrophilic agents such as meropenem is markedly increased, leading to lower or highly variable initial plasma concentrations despite the administration of identical doses. Pharmacokinetically, the hydrophilic nature of meropenem may lead to a lower tissue-to-plasma concentration ratios at certain infection sites, particularly in solid tissues, despite adequate systemic exposure.^{25,26}

Meropenem lacks functional groups that are readily metabolized by hepatic enzymes (e.g., cytochrome P450) and therefore, undergoes minimal biotransformation. The drug is predominantly excreted unchanged via glomerular filtration and tubular secretion. As a result, any reduction in glomerular filtration rate, such as that occurring in AKI, directly leads to a decrease in systemic clearance. Pharmacokinetically, this manifests as a prolonged elimination half-life, which promotes drug accumulation following repeated dosing, as reflected by increased C_{max} and C_{trough} concentrations.^{27,28} These pharmacokinetic consequences were clearly demonstrated in the present PBPK simulation, wherein the predicted C_{trough} remained markedly elevated throughout the dosing interval, consistent with significantly impaired renal elimination.

PK/PD Discordance of Meropenem in Critically Ill Patients

In this case, PBPK simulation demonstrated markedly elevated meropenem exposure despite complete pharmacodynamic target attainment (100% fT>MIC) in a critically ill child with acute kidney injury. Discordance between pharmacokinetic (PK) and pharmacodynamic (PD) targets has increasingly been recognized in critically ill patients receiving beta-lactam antibiotics, including meropenem. This discordance refers to a clinical scenario in which pharmacodynamic targets, most commonly the proportion of time that free drug concentrations remain above the minimum inhibitory concentration (fT>MIC) are achieved or exceeded, while overall drug exposure is excessive and associated with an increased risk of toxicity.^{29,30}

Meropenem is a time-dependent antibiotic, and $fT > MIC$ is widely accepted as the primary pharmacodynamic (PD) target for antibacterial efficacy. However, this target defines only the minimum exposure required for antibacterial activity and does not incorporate upper exposure thresholds related to safety. In critically ill patients, particularly those with AKI, reduced renal clearance and prolonged elimination half-life can result in persistently elevated trough concentrations (C_{trough}) and cumulative drug exposure (AUC). As a result, $fT > MIC$ may reach 100% or more, reflecting not optimized antimicrobial therapy but rather supratherapeutic drug exposure.^{28,30,31}

This PK/PD discordance is further amplified by the pathophysiological changes associated with critical illness. Sepsis-related capillary leak and fluid resuscitation initially increase the volume of distribution of hydrophilic drugs such as meropenem, while subsequent or concurrent renal dysfunction markedly reduces clearance. Additionally, low intrinsic plasma protein binding and sepsis-associated hypoalbuminemia further increase the unbound fraction of meropenem, leading to higher pharmacologically active unbound drug concentrations.^{15,16,18}

This discordance is particularly relevant, as meropenem-associated neurotoxicity (including seizures, encephalopathy, altered mental status, and movement disorders) has been associated with an increased risk with excessive systemic exposure and elevated trough concentrations, rather than with pharmacodynamic target attainment alone. Importantly, supratherapeutic drug concentrations do not uniformly result in neurotoxicity; however, patients with impaired or unstable renal function appear to be at greater risk. The mechanisms underlying β -lactam-associated neurotoxicity are not fully understood but are thought to involve central nervous system excitotoxicity through several pathways, including inhibition of γ -aminobutyric acid type A ($GABA_A$) receptor activity, reduced presynaptic GABA release, and interference with benzodiazepine receptor function. Structural similarities between the β -lactam ring and GABA may further facilitate direct interaction with the $GABA_A$ receptor complex, thereby promoting neuronal hyperexcitability.^{32,33}

In parallel, TDM has been increasingly implemented over the past decade to guide antimicrobial dosing in intensive care settings, whereas marked pharmacokinetic variability is commonly observed. TDM has primarily been used to optimize antimicrobial exposure, typically through dose adjustments based on steady-state trough concentrations obtained 24–48 hours after treatment initiation or through Bayesian dosing approaches for β -lactams. While dose-dependent neurotoxicity may theoretically limit dose escalation, reported toxicity thresholds for β -lactams are generally high, thereby permitting the use of higher empirical dosing regimens that can subsequently be refined through TDM.³² Recent studies suggest that TDM may also contribute to minimizing toxicity for certain antimicrobial agents. In a retrospective cohort of 93 patients (McDonald, *et al.* 2016), TDM-guided administration of higher-than-licensed doses of meropenem or piperacillin/tazobactam was not associated with excessive drug-related toxicity, despite mean daily doses being approximately 40% higher in the high-dose groups.³⁴ Nevertheless, a major limitation to the widespread implementation of TDM for toxicity prevention remains the absence of well-established and universally accepted toxicity thresholds for β -lactams.^{34,35}

Microbiome Effects of Supratherapeutic Meropenem Exposure

Supratherapeutic exposure to meropenem may have clinically relevant effects on the host microbiome, particularly in critically ill patients. As a broad-spectrum carbapenem with potent activity against gram-positive, gram-negative, and anaerobic bacteria, meropenem can profoundly disrupt microbial ecology when systemic and intestinal drug concentrations exceed therapeutic levels. At supratherapeutic concentrations, meropenem exerts broad and non-selective antibacterial pressure, suppressing not only the target pathogen but also beneficial commensal microorganisms within the gut microbiota. This extensive depletion of commensal bacteria may impair gut barrier integrity, alter bile acid metabolism, and disrupt immune homeostasis, leading to prolonged intestinal dysbiosis.^{32,36,37}

Moreover, supratherapeutic antibiotic exposure exerts strong selective pressure on the gut microbiome, thereby facilitating the emergence and propagation of antimicrobial resistance. The intestinal microbiota represents a major reservoir of resistance genes, and excessive carbapenem exposure may favor the selection of resistant subpopulations, including carbapenemase-producing organisms (CPOs). Importantly, these ecological effects may persist long after antibiotic discontinuation, contributing to the long-term propagation of antimicrobial resistance at both the individual and population levels.^{39–41} These microbiome-related consequences underscore a critical limitation of relying solely on pharmacodynamic target attainment. Although supratherapeutic exposure may ensure sustained $fT > MIC$ target attainment and apparent microbiological efficacy, it does not confer additional clinical benefit and may instead exacerbate microbiome disruption and resistance selection. This observation reinforces the concept of a discordance between PK/PD target attainment and broader safety and ecological considerations, in which pharmacodynamic goals are achieved at the expense of microbial homeostasis and antimicrobial stewardship.^{38,40,42,43}

Conclusion

This case report demonstrates that in critically ill pediatric patients with sepsis and renal impairment, standard meropenem dosing may result in substantial drug accumulation and supratherapeutic exposure. Although pharmacodynamic targets were fully achieved, the PBPK simulation suggests that such excessive exposure may increase the risk of adverse effects and microbiome disruption without conferring additional clinical benefit. These findings highlight the limitations of relying solely on $fT > MIC$ to guide dosing in patients with unstable renal function. PBPK modeling may serve as a valuable adjunct to clinical judgment and therapeutic drug monitoring by helping to anticipate extreme exposures and support more individualized dosing decisions.

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Multi-Scale Mechanisms of *Phaleria macrocarpa* in Liver Fibrosis: From Hepatic Stellate Cell Reprogramming to Systems Pharmacology Insights

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Abstract

Liver fibrosis represents a central pathological process that bridges chronic liver injury to cirrhosis and hepatocellular carcinoma, yet effective therapies across all etiologies remain limited. *Phaleria macrocarpa* (mahkota dewa), a traditional Indonesian medicinal plant, has emerged as a promising candidate due to its rich phytochemical diversity and potential polypharmacological effects. This review aims to integrate current evidence at the molecular, cellular, and systems levels to elucidate the anti-fibrotic potential of *P. macrocarpa*, with particular focus on hepatic stellate cell (HSC) biology. We systematically synthesize findings from phytochemical profiling, *in vivo* fibrosis models, early clinical observations, and recent systemic pharmacology studies, including data on standardized fractions such as Proliverenol. Available evidence consistently demonstrates that *P. macrocarpa* attenuates key drivers of fibrosis, including oxidative stress, inflammatory signaling (e.g., NF- κ B/TNF- α), and pro-fibrogenic mediators such as TGF- β 1, thereby reducing fibrotic burden in experimental models. At the compound level, constituents such as gallic acid and mangiferin provide proof-of-principle for direct modulation of HSC activation and fibrogenesis-related pathways. However, a critical mechanistic gap remains: current studies primarily support suppression of the fibrogenic microenvironment rather than direct reprogramming of HSCs toward quiescence, apoptosis, or senescence. Recent network pharmacology analyses highlight key regulatory hubs (e.g., RELA, PTGS2, SIRT1, GSK3B), suggesting that *P. macrocarpa* operates through multi-target mechanisms intersecting inflammatory, metabolic, and survival pathways. We propose a multi-scale framework that positions *P. macrocarpa* as a systems-pharmacology-driven anti-fibrotic candidate and emphasize the need for future studies targeting HSC-specific phenotypes, integrating single-cell omics, and providing translational validation. Advancing this plant from a hepatoprotective agent to a fibrosis-focused therapeutic will require direct mechanistic interrogation of stellate cell state transitions and rigorous clinical evaluation.

Keywords: *Phaleria macrocarpa*, liver fibrosis, hepatic stellate cells, systems pharmacology, natural products

Abstrak

Fibrosis hati merupakan proses patologi sentral yang menjembatani cedera hati kronis menuju sirosis dan karsinoma hepatoseluler, namun terapi efektif lintas etiologi masih terbatas. *Phaleria macrocarpa* (mahkota dewa), tanaman obat tradisional Indonesia, muncul sebagai kandidat potensial karena keragaman fitokimia dan efek polifarmakologinya. Tinjauan ini bertujuan mengintegrasikan bukti terkini pada tingkat molekuler, seluler, dan sistem untuk menjelaskan potensi antifibrotik *P. macrocarpa*, dengan fokus khusus pada biologi sel stelata hepatic (*hepatic stellate cells*/HSC). Studi ini

menyintesis temuan dari profil fitokimia, model fibrosis *in vivo*, observasi klinis awal, dan pendekatan farmakologi sistemik terkini, termasuk data fraksi terstandarisasi seperti Proliverenol. Bukti yang tersedia menunjukkan bahwa *P. macrocarpa* mampu menekan pendorong utama fibrosis, termasuk stres oksidatif, sinyal inflamasi (misalnya NF- κ B/TNF- α), dan mediator profibrogenik seperti TGF- β 1, sehingga mengurangi derajat fibrosis pada model eksperimental. Pada tingkat senyawa, komponen seperti *gallic acid* dan mangiferin memberikan bukti awal terhadap modulasi langsung aktivasi HSC dan jalur fibrogenesis. Namun demikian, kesenjangan mekanistik utama masih terdapat pada terbatasnya bukti mengenai kemampuan *P. macrocarpa* dalam mereprogram HSC menuju keadaan *quiescent*, apoptosis, atau *senescence*. Analisis farmakologi jaringan terbaru menyoroti target regulator utama seperti RELA, PTGS2, SIRT1, dan GSK3B yang menunjukkan mekanisme multitarget pada jalur inflamasi, metabolik, dan kelangsungan hidup sel. Tinjauan ini mengusulkan kerangka multiskala yang menempatkan *P. macrocarpa* sebagai kandidat antifibrotik berbasis farmakologi sistem serta menekankan perlunya penelitian lanjutan yang berfokus pada fenotipe spesifik HSC, integrasi pendekatan *single-cell omics*, dan validasi translasi klinis. Untuk mengembangkan tanaman ini dari sekadar agen hepatoprotektif menjadi terapi yang berfokus pada fibrosis, diperlukan penyelidikan mekanistik langsung terhadap transisi keadaan sel selata serta evaluasi klinis yang ketat.

Kata kunci: *Phaleria macrocarpa*, fibrosis hati, *hepatic stellate cells*, farmakologi system, produk alami

Introduction

Liver fibrosis is not a niche histopathological curiosity; it is the convergent repair programme underlying a very large share of global chronic liver disease. Global analyses estimate more than 58 million incident cases and roughly 1.43 million deaths from cirrhosis and other chronic liver diseases in 2021.¹ Liver cancer remains a major downstream consequence, with about 0.87 million new cases and about 0.76 million deaths worldwide in 2022.² In practical clinical terms, fibrosis is the biological bridge between persistent liver injury and the later emergence of cirrhosis, portal hypertension, hepatic decompensation, and hepatocellular carcinoma.³

The therapeutic landscape is starting to move, but it remains incomplete. The U.S. Food and Drug Administration approved *resmetirom* (Rezdiffra) in March 2024 for adults with noncirrhotic nonalcoholic steatohepatitis (NASH) and moderate-to-advanced fibrosis, and approved *semaglutide* (Wegovy) in 2025 for metabolic dysfunction-associated steatohepatitis (MASH) with moderate-to-advanced fibrosis.^{4,5} These approvals are important because they disprove the earlier claim that no approved fibrosis-directed therapies exist. Yet, they do not solve the broader problem: there is still no universally effective, pan-etiology therapy that directly reprograms hepatic stellate cell state across viral, alcoholic, cholestatic, and metabolic fibrosis.

That is precisely why natural products remain attractive. *Phaleria macrocarpa* (mahkota dewa) has a long history of medicinal use in Indonesia, and has traditionally been associated with indications related to inflammation, metabolic dysfunction, and liver disorders.⁶ What makes this plant particularly interesting for fibrosis is not only its ethnopharmacological relevance, but also its diverse phytochemical composition spans, include benzophenone glycosides, xanthenes, flavonoids, lignans, phenolics, and saponin-containing fractions, creating the conditions for genuine polypharmacology rather than a single-target effect.⁷

The critical gap is that the literature still sits in disconnected layers. Whole-extract studies have shown antioxidant, anti-inflammatory, and antifibrotic signals *in vivo*, while recent systems pharmacology analyzes have identified potential network-level targets for Proliverenol. However, a comprehensive integration across hepatic stellate cell biology, fibrosis-signaling pathways, and systems-level target architecture is still missing.⁸ The clearest evidence of this gap comes from the most directly relevant rat fibrosis study, which explicitly acknowledged that HSC activation, tissue inhibitor of metalloproteinases (TIMP) regulation, and the precise mechanism of matrix remodeling were not determined. This review therefore provides a multi-scale mechanistic framework linking the phytochemical landscape of *Phaleria macrocarpa* to hepatic stellate cell

reprogramming, inflammatory and oxidative signaling, extracellular-matrix dynamics, and network pharmacology, while clearly distinguishing between findings supported by current evidence and those that remain hypothetical.

Phytochemical Landscape

The chemistry of *Phaleria macrocarpa* is sufficiently diverse to justify a systems biology perspective. Early phytochemical investigations of the fruit identified icaraside C3, phalerin, and mangiferin, while later studies isolated mahkoside A and mahkoside B as benzophenone glucopyranosides.⁹ Independent phytochemical screening also identified flavonoids, broader phenolics, tannin-related constituents, and saponin glycosides, and plant's lignan stereochemistry has been characterized as well.¹⁰ Taken together, the plant is not a single-compound botanical; it is a chemically layered scaffold library.

This diversity is important because the recent Proliverenol study moved the field from “the plant contains bioactives” to “a defined proprietary fraction has traceable chemistry and network-predicted targets”. The 2026 pharmacoinformatics report described Proliverenol as a phalerin-rich preparation and linked the fraction to inflammatory, metabolic, and survival hubs, including RELA, PTGS2, SIRT1, GSK3B, and MCL1.⁸ Even though that study focused on metabolic dysfunction-associated fatty liver disease (MAFLD) rather than fibrosis *per se*, these nodes are deeply relevant to fibrogenic liver remodeling.

Table 1. Phytochemical constituents and standardized fractions of *Phaleria macrocarpa* with putative antifibrotic relevance across molecular targets and hepatic stellate cell biology

Candidate constituent or fraction	Chemical class	What is directly known	Why it matters for liver fibrosis
Proliverenol	Standardized fruit-derived bioactive fraction; recent work places phalerin among dominant constituents and identifies inflammatory or metabolic targets.	In rodent liver-injury and fibrosis models, Proliverenol or closely related aqueous fruit fractions lowered transaminases, reduced oxidative stress, decreased transforming growth factor (TGF)-β1, and reduced fibrotic area. Network pharmacology linked the fraction to RELA, PTGS2, SIRT1, GSK3B, and MCL1.	Best current “product-level” evidence base for <i>P. macrocarpa</i> as an antifibrotic candidate, but still lacks on direct HSC-state assays. ⁸
Phalerin	Benzophenone glucoside	Originally isolated from the fruit; structurally revised as a benzophenone glycoside. Recent Proliverenol profiling described it as the most abundant constituent.	Strong marker compound for standardization and is likely a contributor to anti-inflammatory polypharmacology, but no fibrosis-specific mechanistic study was retrieved for phalerin alone. ⁹
Gallic acid	Phenolic acid	Gallic acid attenuated experimental liver fibrosis <i>in vivo</i> and directly targeted activated HSCs <i>in vitro</i> , reducing their proliferation or activation while inducing necrosis or necroptosis in activated stellate cells.	This represent the clearest proof-of-principle that a <i>P. macrocarpa</i> -associated small molecule can act directly on the core effector cell of fibrosis. ¹¹

Candidate constituent or fraction	Chemical class	What is directly known	Why it matters for liver fibrosis
Mangiferin	Xanthone C-glycoside	Mangiferin is a canonical constituent isolated from <i>P. macrocarpa</i> fruits and has demonstrated independent antifibrotic efficacy in liver injury models, primarily through the suppression of NF-κB-mediated fibrogenesis and HSC activation.	Provides a biologically credible mechanism by which <i>P. macrocarpa</i> chemistry engages the Nrf2/NF-κB networks and metabolism-linked fibrosis pathways. ^{9,12}
Mahkoside A and B	Benzophenone glucopyranosides	Isolated from nut shell or fractionated plant material as defined benzophenone glycosides.	Their fibrosis-specific roles are unknown, but the benzophenone family underscores that <i>P. macrocarpa</i> is chemically distinct from the more familiar flavonoid-dominant hepatoprotective botanicals. ¹³
Lignan-containing fractions	Lignans	Lignan stereochemistry and tissue distribution have been characterized in the species.	This is important because lignans often modulate redox and inflammatory networks, yet <i>P. macrocarpa</i> lignans remain largely unexplored in fibrosis-specific assays. ¹⁴

From a medicinal chemistry perspective, the compounds summarized in this table suggest that *P. macrocarpa* contains at least three pharmacological families relevant to fibrosis: redox-active phenolics and xanthenes, benzophenone glycosides that modulate inflammatory signaling, and minor constituents with potential metabolic or transcriptional effects. What remains lacking is not additional cataloguing of chemistry, but rather activity-guided fractionation against fibrosis-relevant phenotypes such as alpha-smooth muscle actin (α-SMA) repression, collagen type 1 alpha 1 (COL1A1) suppression, lipid-droplet restoration, peroxisome proliferator-activated receptor gamma (PPARγ) induction, and HSC senescence or apoptosis.⁹

Fibrosis Biology Across Scales

Liver fibrosis begins upstream of the extracellular matrix. Injured or steatotic hepatocytes release signals that activate Kupffer cells and hepatic stellate cells, while macrophage-derived TNF-α and gut-liver axis signaling through toll-like receptor 4 (TLR4) amplify the transition from sterile injury to fibrogenic inflammation.¹⁵ Experimental studies have demonstrated that conditioned medium from steatotic hepatocytes activates human HSCs, enhances phosphatidylinositol 3-kinase (PI3K) signaling, and upregulates TGF-β-, TIMP-, matrix metalloproteinase (MMP)-, and NF-κB-dependent profibrogenic programs. In nonalcoholic steatohepatitis (NASH) models, Kupffer cell-derived TNF-α is essential for fibrosis progression, while TLR4 signaling enhances TGF-β responsiveness during hepatic fibrogenesis.¹⁶

At the center of disease progression is the hepatic stellate cell. Activated HSCs are the key mesenchymal drivers of hepatic scar formation; however, they are not irreversibly fixed in this state. Fibrosis resolution may involve apoptosis, senescence, or reversion of activated HSCs into a quiescent-like, inactivated state. This distinction is crucial for this review, because

the most ambitious interpretation of *Phaleria macrocarpa* is not merely “less injury” but “HSC reprogramming”. Existing evidence indicates that such reprogramming is biologically feasible.¹⁷ The multi-scale architecture of liver fibrogenesis, spanning hepatocyte injury, immune activation, stellate-cell transition, and extracellular matrix remodeling, is summarized in **Figure 1**.

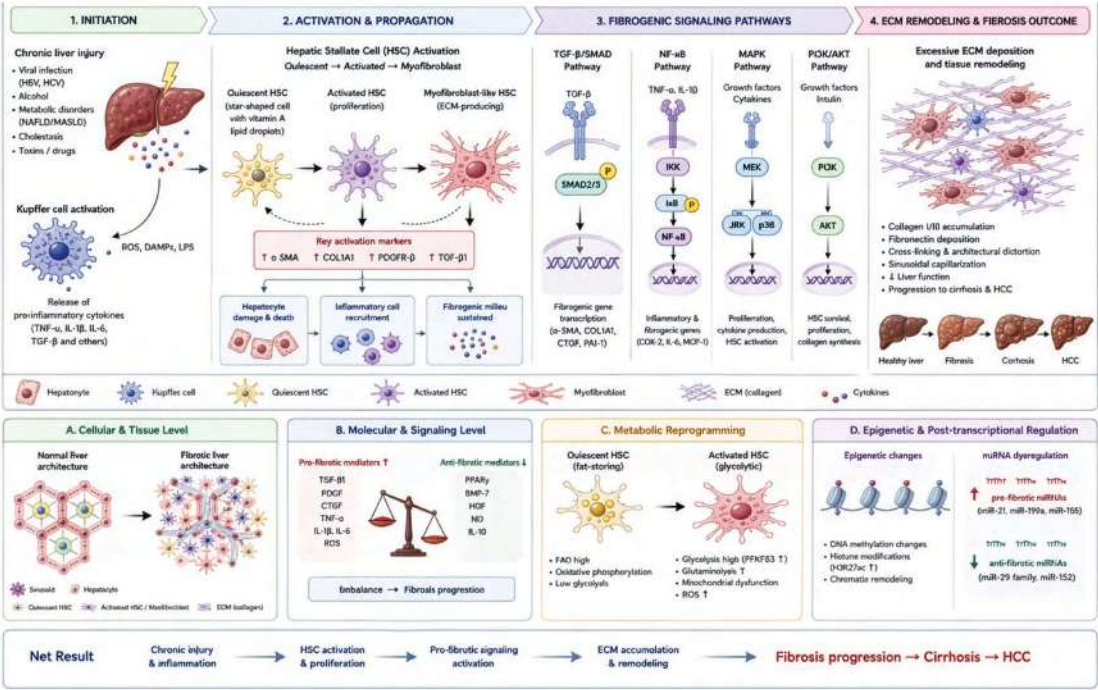


Figure 1. Multi-scale pathogenesis of liver fibrosis (baseline framework)

The canonical signaling axis in liver fibrogenesis remains the TGF- β /SMAD pathway. Smad7 overexpression blocks HSC activation and limits liver fibrosis, underscoring the central role of TGF- β /SMAD signaling.^{18,17} NF- κ B also played a nuanced role: it supports HSC proliferation and survival and is activated by inflammatory inputs including TNF- α , LPS, and TLR4-linked pathways. Meanwhile, steatosis-related fibrogenesis recruits PI3K/AKT as part of hepatocyte-to-HSC crosstalk. In other words, the core pro-fibrotic architecture is not a single pathway but an interlocked module linking TGF- β /SMAD, NF- κ B, and PI3K/AKT.^{19,20}

More recent studies have added a metabolic layer. Activated HSCs are not merely transcriptionally distinct; they are metabolically rewired. PFKFB3-dependent glycolysis drives activation in both mouse and human HSCs models, Wnt signaling promotes HSC glycolysis through LDH-A/HIF-1 α , and glycolysis can even coordinate fibrogenic extracellular-vesicle release to spatially amplify scarring.²¹ Conversely, PKM2 tetramerization and mitochondrial pyruvate carrier inhibition both attenuate fibrosis in experimental models, showing that HSC metabolism is now a therapeutic axis rather than a bystander phenomenon.²²

Extracellular matrix remodeling is equally dynamic. HSCs and liver myofibroblasts are major sources of collagen and also key regulators of MMP/TIMP balance.²³ During HSC activation, MMP expression tends to fall while TIMPs increase,

thereby promoting extracellular matrix accumulation. TNF- α can stimulate both MMP and TIMP expression, whereas TGF- β 1 preferentially induces TIMPs, tilting the balance away from matrix degradation. MMP-13 is particularly importance in rodents, as it promotes recovery and can accelerate cirrhosis resolution; however, its interpretation depends on context and cannot be simplified to the notion that either increased or decreased expression is universally beneficial.²⁴

Mechanistic Evidence for *Phaleria macrocarpa* and Proliverenol

The liver-focused *Phaleria macrocarpa* literature is limited, yet it is more coherent than it first appears. One study addressed ethanol-induced hepatotoxicity, two studies directly evaluated rodent fibrosis models, one recent clinical report examined NAFLD/MASH-related liver damage, and a 2026 systems pharmacology study proposed multi-target mechanisms for Proliverenol. Taken together, these studies suggest a consistent mechanistic axis characterized by inflammatory suppression and redox normalization upstream of reduced pro-fibrogenic signaling.²⁵ A multi-target mechanistic framework integrating these observations across inflammatory, oxidative, fibrogenic, and stellate-cell regulatory axes is illustrated in Figure 2.

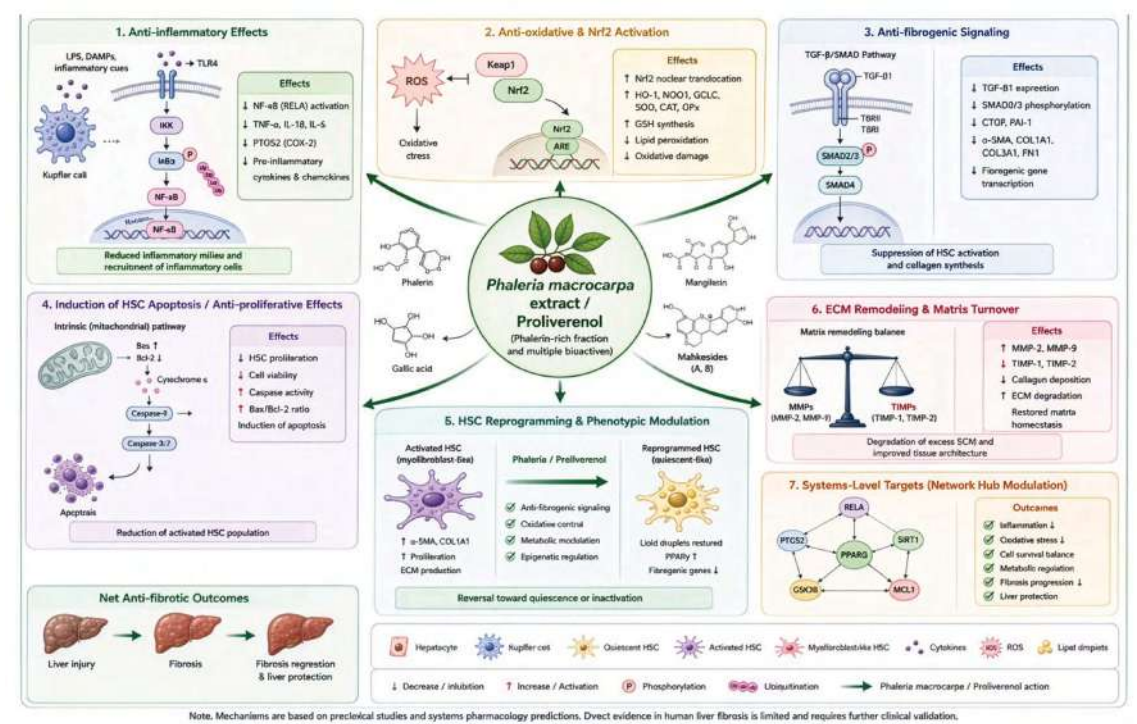


Figure 2. Multi-target mechanisms of *Phaleria macrocarpa*/Proliverenol in liver fibrosis

Table 2. Preclinical and clinical evidence supporting the antifibrotic effects of *Phaleria macrocarpa* and Proliverenol across experimental models and human studies

Study and model	Intervention	Main end points	Main findings	What the study really proves
Ethanol-induced hepatotoxicity model, 2016	Standardized Proliverenol fraction	NF-κB, TNF-α, caspase-8, ALT leakage	Proliverenol down-regulated NF-κB/TNF-α/caspase-8 signaling and showed hepatoprotective activity.	Strong support for anti-inflammatory and cytoprotective signaling; not a fibrosis-specific HSC study. ²⁵
CCl ₄ -induced fibrosis in rats, 2018	Water extract of Proliverenol-related fruit preparation (50–150 mg/kg); NAC comparator	AST, ALT, ALP, fibrosis area, MDA, GSH/GSSG, TNF-α, TGF-β1	Liver enzymes, oxidative stress, inflammatory cytokines, and fibrosis burden improved across treatment groups.	Convincing <i>in vivo</i> antifibrotic signal through redox and inflammatory modulation; HSC effects are indirect. ⁶
CCl ₄ -induced fibrosis in rats, 2020	Proliverenol (75 or 150 mg/kg); silymarin comparator	ALT, AST, ALP, fibrosis area, MDA, GSH/GSSG, TGF-β1, MMP-13	Proliverenol improved biochemistry, lowered TGF-β1, improved oxidative stress, and reduced fibrotic area; MMP-13 staining declined.	Confirms antifibrotic activity, but the authors explicitly state that HSC activation, TIMPs, and detailed MMP regulation were not determined. ²⁶
NAFLD patient, 2025	Proliverenol supplementation; registry shows 500 mg caplets in an 80-subject interventional study; journal abstract highlights 1,000 mg twice daily as effective	Liver-function improvement and safety	Early clinical signal of improved liver function with acceptable safety in NAFLD/MASH-related liver damage.	Valuable translational signal, but fibrosis-specific endpoints, biopsy data, and detailed public reporting remain limited. ²⁷
Proliverenol pharmacoinformatics, 2026	Untargeted phytochemical profiling plus target fishing, PPI, enrichment, docking	Network hubs and pathway-level predictions	Phalerin-rich Proliverenol linked to RELA, PTGS2, SIRT1, GSK3B, and MCL1, supporting anti-inflammatory, metabolic, and cytoprotective polypharmacology.	Strong systems hypothesis generation; not yet direct experimental validation in fibrosis-relevant HSC models. ⁸

Across the animal studies, the most reproducible signals are anti-inflammatory and antioxidative. The 2018 study showed improvement in TNF-α, TGF-β1, MDA, the GSH/GSSG ratio, histological fibrosis, and liver enzymes, while the 2020 study similarly reported lower MDA and TGF-β1 levels together with decreased fibrosis area. The earlier ethanol-hepatotoxicity study also converged on NF-κB/TNF-α/caspase-8 suppression. The simplest mechanistic interpretation is that *P. macrocarpa* dampens the inflammatory-redox microenvironment that normally sustains HSC activation,^{5,21,22}

This interpretation is more strongly supported by the available evidence than claims of direct HSC reprogramming. The *in vivo* findings are consistent with reduced HSC activation, indicated by decreased TGF-β1 and lower fibrotic burden, but neither study directly measured α-SMA expression, COL1A1 transcription in isolated HSCs, lipid droplet restoration, PPARγ

induction, or stellate-cell senescence markers. In fact, the 2020 authors explicitly stated that HSC activation by *Phaleria macrocarpa* was not determined and that the mechanism involving TIMPs and MMPs remained unclear.²⁶ Accordingly, the most evidence-based conclusion at present is suppression of HSC-activating conditions, not yet demonstrated HSC state reversal.

This distinction becomes even more important in the apoptosis/senescence literature. Genuine HSC reprogramming has already been achieved experimentally by several strategies outside the *Phaleria macrocarpa* field. Re-expression of PPAR γ can drive phenotypic reversal and apoptosis of activated HSCs, lineage-specific transcription factors can generate inactivated HSCs during fibrosis resolution, IL-10 can promote HSC senescence, doxazosin can reverse the fibrogenic phenotype while inducing senescence, and a 2024 culture method even restored activated HSC lines to a lipid-droplet-rich quiescent state.²⁸ None of these readouts has yet been demonstrated for *P. macrocarpa* itself. A conceptual model of hepatic stellate cell state transitions, including apoptosis, senescence, and reversion to a quiescent-like phenotype, and the hypothesised role of *Phaleria macrocarpa* in this process, is presented in **Figure 3**.

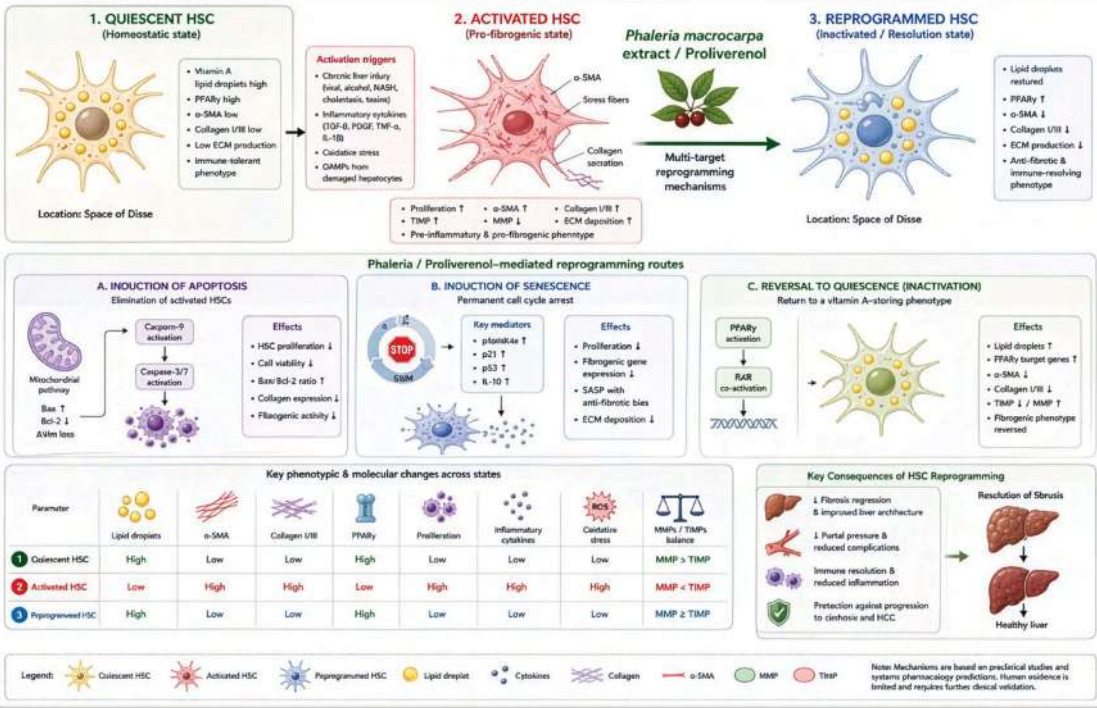


Figure 3. Hepatic stellate cell reprogramming by *Phaleria macrocarpa*/Proliverenol

Where *Phaleria macrocarpa* becomes intellectually stronger is at the compound level. Gallic acid, a constituent associated with the plant, directly attenuates fibrosis *in vivo* and selectively kills activated HSCs through necrosis or TNF- α -mediated necroptosis.¹⁰ Mangiferin, another canonical *P. macrocarpa* constituent, suppresses collagen accumulation and HSC activation in liver-injury models through inflammatory and oxidative signaling.^{29,30} These two compounds are significant because they demonstrated that the plant's chemistry is not merely hepatoprotective in a generic sense; it contains molecules with experimentally validated relevance to fibrosis biology and stellate-cell regulation.^{11,31,32}

The MMP-13 story requires special care. In the 2020 rat fibrosis study, Proliverenol reduced MMP-13 staining alongside improvements in fibrosis-related parameters. At first glance, this appears paradoxical, since MMP-13 can promote fibrosis resolution. However, the paper itself helps explain the issue: in chronic injury, MMP-13 may also rise as part of an inflammatory and injury-responsive remodeling milieu. In the absence of parallel measurements for TIMP-1, TIMP-2, and direct markers of collagen turnover, a reduction in MMP-13 staining cannot be interpreted in isolation. Mechanistically, this findings suggest that *Phaleria macrocarpa* influences extracellular matrix (ECM) remodeling; however, current data do not yet reveal whether it enhances resolution, suppresses inflammatory remodeling, or both.²⁶

Systems Pharmacology, Comparison, and Translational Barriers

The 2026 Proliverenol study provides the first network-level framework extending beyond phenotypic observations from rodent models. The identified regulatory hubs—RELA, PTGS2, SIRT1, GSK3B, and MCL1—are biologically plausible for fibrosis, as they reside at the intersection of inflammation, metabolic control, and cell-survival signaling. Importantly, these hubs were identified in the context of MAFLD and should not be interpreted as fibrosis-specific targets. A fibrosis-focused network centred on the user's proposed nodes—TGF- β 1, COL1A1, MMP9, and PPAR γ —would therefore be a logical next step rather than a completed result. That next step is especially credible because other *P. macrocarpa* fractions have already yielded PPAR γ -binding candidates *in silico*, suggesting that the plant's chemistry can intersect with the validated quiescence-supporting transcriptional circuitry of HSCs.⁸

This is where omics integration becomes genuinely powerful. Single-cell and multi-modal studies now define conserved activation trajectories, transcriptomic states, and chromatin programs in human and mouse HSCs across liver injuries. Consequently, future network analyses of *Phaleria macrocarpa* should extend beyond target fishing and molecular docking; they should be overlaid onto real HSC state atlases to ask whether Proliverenol predicts deactivation, senescence, inflammatory suppression, or matrix-remodeling bias in specific stellate-cell subpopulations.³³

In a comparative frame, *Phaleria macrocarpa* occupies an interesting middle ground between established hepatoprotective botanicals and still-emerging fibrosis candidates. Silymarin already has clear evidence for reducing Kupffer cell activation, α -SMA, and TGF- β 1 in fibrotic rat models and for suppressing HSC activation in diet-associated fibrosis.³⁴ Curcumin goes even further mechanistically: it inhibits HSC activation and angiogenic behavior, restores intracellular lipid droplets, blocks CXCL12/CXCR4-linked migration, and interferes with sterol regulatory element-binding protein (SREBP)2-associated stellate-cell metabolic signaling.³⁵ *Phaleria macrocarpa* overlaps with both in anti-inflammatory and antioxidant architecture, but its distinctive feature is its phalerin-rich benzophenone chemistry and the existence of an early product-level human signal through Proliverenol.^{36,37}

The translational barriers are equally clear. Although the phytochemical composition of *Phaleria macrocarpa* can be standardized through defined marker compounds and fractionation approaches, its pharmacokinetic profile remains insufficiently characterized. The 2020 Proliverenol paper described a defined subcritical-water extraction workflow, and the 2026 profiling paper provides a stronger basis for future quality control, but that is not yet equivalent to knowing which constituents reach the fibrotic liver at active concentrations.^{7,22} Mangiferin, for example, shows measurable but low plasma exposure in humans after oral dosing,²⁸ and gallic acid disposition can be substantial but formulation-sensitive.³⁸ Second, sponsor-led development has dominated the field so far, which makes independent replication especially important. Third, the available safety signals are encouraging but still preliminary: a rat study of *P. macrocarpa* leaves reported normal SGOT/SGPT levels and no histological liver toxicity, and the 2025 NAFLD report described good tolerability, but chronic fibrosis-oriented toxicology and drug-interaction studies remain sparse.^{26,23}

The clinical gap is therefore not “zero evidence”, but “insufficiently deep evidence”. An 80-subject interventional registry

entry and an accompanying journal report suggest that Proliverenol may improve liver function in NAFLD/MASH-related injury, which is valuable. However, those data do not yet establish fibrosis regression, resolve dose-response independently of sponsorship, or provide the biopsies, elastography changes, or validated serum fibrosis biomarkers required for a true antifibrotic claim.

Future Perspectives and Conclusion

The most promising future direction is the development of a fibrosis-focused research framework. This means testing purified constituents and activity-guided fractions directly in primary human HSCs and well-phenotyped stellate-cell systems, with readouts that directly address the underlying mechanistic questions: α -SMA, COL1A1, TGFB β 1/SMAD2/3, RELA activity, lipid droplet recovery, PPAR γ induction, senescence markers, apoptosis versus necroptosis, and MMP/TIMP balance. Once those data exist, AI-assisted target prioritization and network pharmacology can become genuinely informative rather than merely descriptive, especially when integrated with emerging single-cell transcriptomic and chromatin accessibility atlases of HSC activation states.³³ A forward-looking framework integrating emerging technologies and translational strategies for *Phaleria macrocarpa* development is presented in Figure 4.

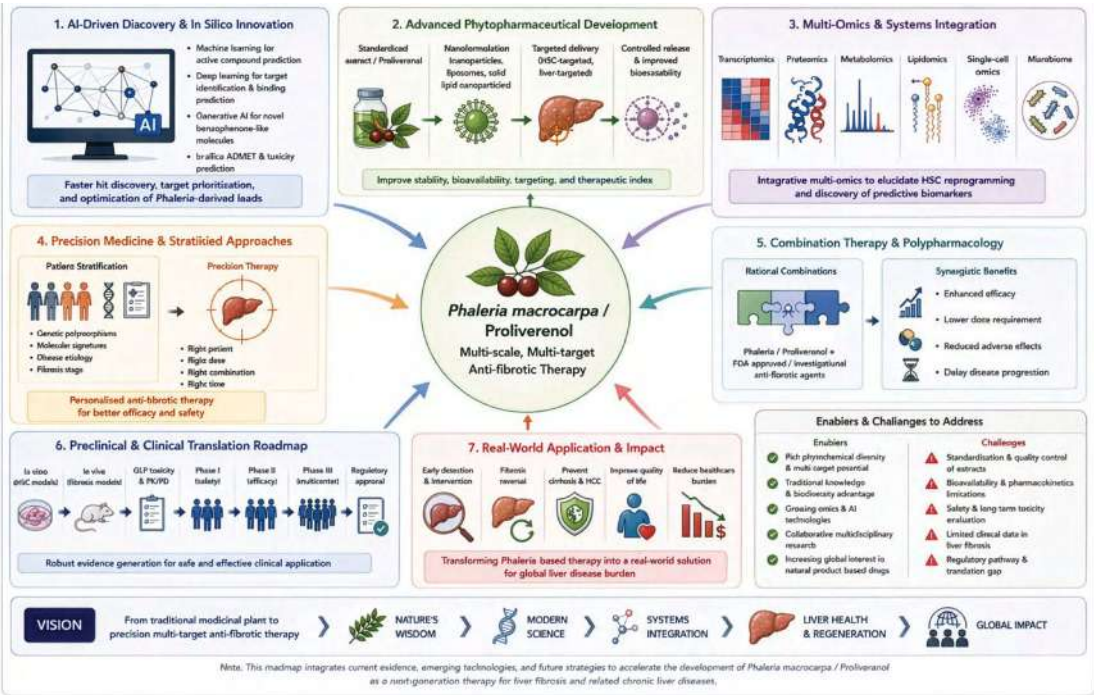


Figure 4. Future perspective of *Phaleria macrocarpa*/Proliverenol in liver fibrosis

Nanoformulation strategies warrant further investigation. If mangiferin-like or phalerin-rich fractions are part of the active antifibrotic principle, formulation strategies will play a critical role in determining translational success, since bioavailability, tissue distribution, and metabolic stability remain major challenges for plant-derived polyphenolic compounds.³⁹ Precision-medicine framing will also matter: a future *Phaleria macrocarpa* program should probably treat metabolic fibrosis, cholestatic fibrosis, and toxin-induced fibrosis as related but distinct endotypes, rather than assuming one extract behaves identically across all etiologies.⁴⁰

The most defensible overall conclusion is therefore a balanced one. *Phaleria macrocarpa* already has a credible antifibrotic foundation. Rodent fibrosis studies show reduced oxidative stress, lower TGF- β 1, improved liver biochemistry, and smaller fibrotic burden; an early clinical study suggests potential benefits for liver function; and recent systems pharmacology has identified target networks that align with key inflammatory and metabolic pathways implicated in chronic liver disease. What it does not yet have is direct proof that the extract or Proliverenol can reprogram hepatic stellate cells toward apoptosis, senescence, or quiescence. That gap is not a weakness to hide; it is the paper's real novelty. The most compelling global positioning for this review is that *Phaleria macrocarpa* should now be advanced from a hepatoprotective Indonesian medicinal plant into a fibrosis-focused, HSC-centred, systems-pharmacology candidate, whose next decisive experiments must test stellate-cell state transitions directly.⁶

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Equity, Informed Consent, and Ethical Challenges in Nutrigenetics-Based Precision Nutrition

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Abstract

Background: Precision nutrition represents a paradigm shift from generalized dietary recommendations to individualized interventions based on genetic, metabolic, and environmental profiles, offering significant potential for the prevention and management of chronic diseases. **Methods:** A comprehensive literature search was conducted using PubMed and Google Scholar to evaluate the current landscape of the field. This review analyzed peer-reviewed articles, systematic reviews, and randomized controlled trials published between 2010 and 2025, focusing specifically on the ethical considerations, accessibility, and clinical integration of nutrigenetics. **Results:** Findings indicate that despite its promise, nutrigenetics-based precision nutrition faces substantial limitations. Scientific validity remains inconsistent, particularly within direct-to-consumer (DTC) genetic testing. Ethical concerns are prominent regarding informed consent, which is often reduced to complex digital agreements that obscure data use, privacy risks, and issues related to autonomy in vulnerable populations. Furthermore, equity challenges persist; high costs and digital literacy gaps threaten to transform precision nutrition into an exclusive service. This is compounded by algorithmic biases stemming from the underrepresentation of diverse populations in genomic datasets, which risks generating inaccurate recommendations and exacerbating existing health disparities. **Conclusion:** While nutrigenetics-based precision nutrition offers transformative opportunities for personalized healthcare, its responsible implementation requires strengthened regulatory frameworks, improved genetic literacy among healthcare professionals, transparent consent processes, and inclusive data practices to ensure equitable integration into clinical and public health systems.

Keywords: health inequity, informed consent, ethical challenges, nutrigenetics, precision nutrition

Abstrak

Latar belakang: Nutrisi presisi merupakan pergeseran paradigma dari rekomendasi diet umum menuju intervensi yang disesuaikan dengan profil genetik, metabolik, dan lingkungan individu. Pendekatan ini menjanjikan potensi yang besar dalam pencegahan dan pengelolaan penyakit kronis. **Metode:** Kajian literatur yang komprehensif dilakukan menggunakan basis data PubMed dan Google Scholar, mencakup artikel *peer-reviewed*, tinjauan sistematis, dan uji klinis acak terkontrol yang diterbitkan antara tahun 2010–2025, dengan fokus pada aspek etika, aksesibilitas, dan integrasi klinis nutrigenetika. **Hasil:** Temuan menunjukkan nutrigenetika menjadi landasan penting bagi penerapan nutrisi presisi, meskipun masih terdapat sejumlah keterbatasan yang signifikan. Validitas ilmiah hasil pemeriksaan genetik masih belum konsisten, terutama pada layanan tes genetik langsung kepada konsumen. Permasalahan etika juga menjadi perhatian, khususnya terkait *informed consent* yang sering kali disajikan dalam bentuk perjanjian digital yang kompleks, dapat mengaburkan

risiko penggunaan data dan privasi, serta mempersulit pemahaman penggunaannya terutama pada populasi rentan. Biaya layanan yang tinggi serta kesenjangan literasi digital berpotensi menjadikan nutrisi presisi sebagai layanan yang hanya dapat diakses oleh kelompok tertentu. Hal ini diperparah dengan bias algoritmik akibat kurang terwakilinya kelompok populasi yang beragam dalam basis data genomik, sehingga berisiko menghasilkan rekomendasi yang kurang akurat dan memperlebar kesenjangan kesehatan yang sudah ada. **Kesimpulan:** Meskipun nutrisi presisi berbasis nutrigenetika menawarkan peluang transformatif bagi perawatan kesehatan yang lebih personal, implementasinya memerlukan penguatan regulasi, peningkatan literasi genetik di kalangan tenaga kesehatan, proses *informed consent* yang transparan, serta tata kelola data yang aman dan inklusif. Langkah-langkah ini krusial untuk memastikan integrasi yang etis ke dalam sistem pelayanan kesehatan klinis maupun kesehatan masyarakat.

Kata kunci: kesenjangan kesehatan, persetujuan berdasarkan informasi, tantangan etika, nutrigenetika, nutrisi presisi

Introduction

Precision nutrition represents a transformative shift in healthcare, moving away from “one-size-fits-all” dietary guidelines toward interventions tailored to an individual’s unique genetic, metabolic, and microbiome profiles.¹ By leveraging advancements in nutrigenetics, which examines how genetic variations affect an individual’s response to nutrients, this field offers unprecedented potential for the prevention and management of chronic diseases such as obesity, diabetes, and cardiovascular disease.² However, the transition from research to clinical and commercial practice introduces a complex array of ethical, legal, and social challenges, that must be addressed to ensure the field’s responsible development.

A primary ethical concern is the adequacy of informed consent, particularly regarding the pleiotropic effects of genes. For example, the *APOE* gene is frequently assessed in nutrigenomic testing to inform cardiovascular risk management; however, it is also a major risk factor for Alzheimer’s disease. Research indicates that participants are often not fully informed of these sensitive secondary implications, violating their “right not to know” and potentially causing significant psychological harm.^{3,3} Furthermore, the rise of direct-to-consumer (DTC) genetic testing complicates this landscape, as these services often bypass professional counselling, rely on persuasive marketing, and may lack robust scientific validation for their recommendations.^{4,5}

The high cost of multi-omics profiling and the reliance on digital health tools risk creating a digital divide, where precision nutrition becomes a “boutique” service accessible only to well-resourced populations while excluding socially and economically disadvantaged groups.⁶ Additionally, algorithmic biases persist because many predictive models are trained on datasets predominantly representing European ancestries, which can lead to inaccurate or even harmful recommendations for underrepresented ethnic groups.⁷ To overcome these barriers, the scientific community must prioritize the development of interdisciplinary clinical guidelines, integrated genomic education for healthcare providers, and inclusive data practices to ensure that the benefits of precision nutrition are deployed ethically and equitably for all.

Methods

This narrative review synthesizes current evidence on equity, informed consent, and ethical challenges in nutrigenetics-based precision nutrition, with a focus on clinical implementation and public health implications. A comprehensive literature search was conducted using PubMed and Google Scholar for studies published between 2010 and 2025. Keywords included “nutrigenetics,” “nutrigenomics,” “precision nutrition,” “ethical issues,” “bioethics,” “informed consent,” “equity,” and “health disparities.”

Inclusion criteria comprised peer-reviewed original research articles, review articles, and randomized controlled trials (RCTs) published in English, that addressed nutrigenetics in relation to ethical considerations, informed consent

processes, or issues of equity and access. Articles were critically appraised based on their methodological rigor, relevance to clinical and public health practice, and contribution to ethical discourse. Both empirical and conceptual studies were considered to provide a comprehensive and balanced perspective. The findings were synthesized thematically, focusing on key domains including equity in access to nutrigenetic services, challenges in informed consent, and broader ethical issues in the implementation of precision nutrition.

Results and Discussion

Nutrigenetic-Based Precision Nutrition: Concepts, Potential Benefits, and Risks

Nutrigenetics is the study how individual genetic variations, particularly single-nucleotide polymorphisms (SNPs), influence an individual's physiological response to nutrients and dietary intake.² This scientific field specifically explores how hereditary variants impact the uptake, metabolism, and functional utilization of nutrients within the human body.⁸ In contrast, precision nutrition is a critical component of precision medicine that establishes tailored nutritional guidelines and requirements for specific individuals or subgroups. By integrating complex data from an individual's genotype, phenotype, metabolic biomarkers, and environmental exposures, the precision nutrition provides personalized recommendations designed to optimize health, prevent disease, and delay the progression of chronic conditions.^{2,9}

The concept of gene–diet interaction describes a complex bidirectional relationship where an individual's genetic makeup regulates nutrient usage while bioactive food components simultaneously influence gene expression.¹⁰ This interplay manifests in two primary ways. First, genetic factors influence dietary response, meaning that individuals with different genetic backgrounds may respond differently to the same diet. Second, nutrients can facilitate or inhibit gene transcription by interacting with transcription factors, potentially resulting in altered protein function within metabolic pathways.^{10,11} Applying these concepts is particularly relevant to the management of noncommunicable diseases (NCDs). For example, in metabolic syndrome (MetS), high-fat intake may interact with genetic variants related to lipid metabolism, such as *VEGF*, *CAV-1*, *MC4R*, and *ACC2*, thereby increasing disease risk in genetically predisposed individuals.¹² This interaction allows researchers to identify genetic variants that determine whether specific dietary factors increase or decrease a person's susceptibility to various health risks.

These scientific advancements have paved the way for direct-to-consumer genetic testing (DTC-GT), which allows individuals to access their genetic data through mail-in saliva samples without requiring direct involvement from healthcare institutions.⁴ Initially, nutrigenetics addressed monogenic conditions like phenylketonuria or lactose intolerance, where a single gene has a strong, measurable effect. However, modern research now focuses on complex polygenic traits, such as obesity and type 2 diabetes, which result from interactions between multiple genes and environmental factors.¹³

Nutrigenetics-based precision nutrition offers transformative potential across several areas of health and wellness. In the context of athletic performance and body composition, genetic markers are increasingly utilized to identify individual variations in metabolism, muscle function, and injury susceptibility. For example, the *ACTN3* gene is a known indicator of whether an athlete is genetically predisposed to excel in power-based sprinting or endurance activities. A study involving on athletes in Saudi Arabia reported that genetic insights moderately influenced dietary adjustments, with improved digestion and nutrient absorption being among the most positively perceived outcomes (mean=4.01). Furthermore, athletes in artistic sports reported significant changes in body composition, such as muscle gain or fat loss, following gene-based dietary interventions.¹⁴

In the management of chronic and metabolic disease, nutrigenetics enables more targeted interventions for noncommunicable diseases.¹⁵ A prominent example is the *MTHFR* gene, where the 677TT genotype results in reduced enzyme activity, requiring higher folate intake to manage homocysteine levels and reduce cardiovascular risk.¹⁶ Additionally,

the *FTO* gene is a major risk factor for obesity; individuals with the risk allele (*rs9939609*) tend to have a higher BMI, but studies suggest that high-protein diets or Mediterranean-style diets may help mitigate this genetic predisposition.¹⁷ Adjusting fat intake (saturated fatty acids/SFA vs. polyunsaturated fatty acids/PUFA) based on genetic markers like *APOA2* can also help control weight and metabolic syndrome markers.¹⁸

Nutrigenetic testing may also contribute to the prevention of micronutrient deficiencies. For example, some individuals have a genetic predisposition for poor vitamin D absorption due to variants in the *CYP2R1* or *GC* genes, requiring tailored supplementation to maintain adequate vitamin D status and support bone health. Similarly, variants in the *GSTT1* gene can affect the utilization of vitamin C, placing certain individuals at a higher risk of deficiency if they only follow standard recommended dietary allowance (RDA) guidelines.¹³ Finally, beyond physiological benefits, nutrigenetic testing plays a significant role in consumer empowerment and behavioral change. Individuals may experience increased motivation and a greater sense of validation after learning that their health conditions have a biological basis.¹⁹ Furthermore, awareness of genetic risk factors, such as the *APOE ε4* allele associated with Alzheimer's disease, has been shown to significantly enhance positive health behavior changes, with some studies reporting up to a twofold increase in adherence to healthier lifestyles among informed individuals.^{15,20}

Despite its promise, several significant risks and barriers remain for the wide-scale adoption of nutrigenetics:

a. Limited clinical validity and utility

Many claims made by DTC-GT companies are not yet supported by high-quality scientific evidence. An analysis of 45 companies revealed that only one-third disclosed which genes were used for their predictions, and many variants used show weak associations with the traits being tested. There is a high risk of identifying “false signals,” whereby genetic variants do not meaningfully predict phenotypic outcomes within a complex, multifactorial environment.⁵

b. Ethical and privacy concerns

The rise of online genetic services raises serious concerns regarding data security and the potential misuse of genetic information by insurers, employers, or governments. There is also an ethical concern regarding the population validity of these tests; many commercial tests have not been validated for specific ethnic groups (e.g., populations in Mexico or India), meaning the reported effects of polymorphisms may not be accurate for all users.^{21,22}

c. Psychological impact and misinterpretation

Without proper guidance from health professionals or genetic counselors, consumers may misinterpret their results. High-risk genetic report may cause unnecessary anxiety or foster fatalistic beliefs, whereby individuals perceive limited control over their future health outcomes.¹⁵

d. Professional readiness and economic barriers

Many dietitians and doctors report a lack of confidence and practical training in interpreting complex genetic reports. This educational gap creates a barrier to integrating nutrigenetics into standard clinical practice. The high cost of genetic testing, combined with consultation fees for trained professionals, may limit access among individuals of lower socioeconomic status and potentially widen existing health inequalities.²³

Nutrigenetics-based personalized nutrition has evolved from a tool for monogenic diagnosis into a complex framework for precision health, offering vast potential for disease prevention and performance optimization. However, its current utility is hindered by gaps in scientific validity, inconsistent regulations, and significant ethical challenges. To achieve responsible implementation, nutrigenetic information should be integrated with broader lifestyle and clinical strategies and supported by ongoing professional education to ensure ethical and evidence-based practice.

Informed Consent in Nutrigenetics-Based Precision Nutrition

Recent advances in genomic science have accelerated the growth of nutrigenetic testing, a form of genetic analysis used to

assess how individual genetic variations influence responses to nutrients, metabolism, and the risk of diet-related diseases. Nutrigenetic testing is increasingly marketed as a component of personalized nutrition, offering specialized dietary advice based on an individual's DNA profile.⁵ The primary ethical issues in nutrigenomics center on privacy, autonomy, and informed consent, which should be grounded in genuine understanding rather than a mere digital click.²⁴ Given that genetic data are complex, probabilistic, and sensitive, consumers often struggle to understand both their scientific limitations and the potential risk to data privacy. This challenge is even more pronounced among adolescents, whose legal capacity to provide consent varies across jurisdiction, making meaningful consent a persistent ethical challenge in nutrigenetic testing.²⁵

In the context of DTC nutrigenetic testing, informed consent is often inadequate. Consumers may not fully understand how their genetic data are collected, stored, or shared with third parties, particularly when consent agreements are complex and lack transparency.^{5,26} This undermines the ethical principle that individuals should have meaningful control over their personal information. Moreover, these concerns are amplified in low- and middle-income countries, where regulatory frameworks for data protection may be insufficient. In such contexts, vulnerable populations face a heightened risk of exploitation and misuse of their genetic data.²⁷

A 2019 study evaluating 38 DTC nutrigenetic company websites found that only 8 provided easily accessible genetic information, only 13 required signed informed consent, and only 2 offered pretest consultations. Furthermore, much of the critical information was embedded within legal documents that were difficult even for professionals to understand.²⁸ While these methods may be legally sufficient in some jurisdictions, they do not guarantee meaningful understanding. Consumers are often confronted with lengthy privacy policies, complex technical language, and promotional claims that exaggerate the predictive value of the test.²⁵

Another major challenge concerns data privacy. Genetic data may be stored long term, shared with third parties, or reused for future research and commercial purposes. If consumers do not understand these possibilities, their consent cannot be considered fully informed.²⁵

Table 1. Comparison between ideal informed consent ethical standards and reported practices in DTC nutrigenetic testing^{6,25}

Aspect	Ideal informed consent	Practice in DTC testing
Form of consent	Two-way communication process between participants and professionals.	Consent via “I Agree” click or digital checkbox.
Participant understanding	Participants are given time to ask questions and to ensure comprehension.	Users often agree without reading details.
Language/grammar	Simple, clear, and nontechnical.	Long, legalistic terms and conditions.
Purpose of test	Explained specifically and realistically.	Often packaged with “personalized health” promotions.
Test limitations	Clarified that results are probabilistic and not diagnostic.	Sometimes not prominently explained.
Data privacy	Transparent disclosure of data access, storage duration, and sharing policies.	Information often hidden within privacy policies.
Secondary data use	Clear opt-in/opt-out options provided.	Consent is sometimes bundled into a single click.
Professional support	Access to doctors, genetic counselors, or dietitians.	Generally unavailable.
Right to withdraw	Explained clearly and easy to execute.	Process is often difficult to understand.

When nutrigenetic testing involves adolescents, ethical decision-making becomes more complex. In many legal systems, adolescents are not considered to have full authority to provide independent medical consent. Consequently, formal decisions are typically made by parents, while the minor is involved via assent.²⁹ Consent refers to the legally valid authorization by a competent adult, whereas assent refers to the affirmative agreement of a child or adolescent who may lack full legal authority but can participate in decision-making based on their maturity.³⁰ Conflicts may arise when parents seek testing for purposes such as weight management or athletic performance, while the adolescent prefers not to know the results. Results indicating a predisposition to obesity may negatively impact an adolescent's self-esteem or body image. In nonemergency situations where no immediate medical benefit is expected, parental consent alone may be ethically insufficient. Adolescents should be involved through age-appropriate explanations, and their refusal should be taken seriously.^{29,31}

Nutrigenetic testing is a growing field of personalized health, yet meaningful informed consent remains difficult to achieve. In DTC settings, consent is often reduced to a digital agreement that does not guarantee understanding. For adolescents, the challenge lies in balancing parental authority with the adolescent's developing autonomy through proper assent procedures. Future regulatory frameworks should emphasize transparency, evidence-based claims, and age-sensitive consent models.

Ethical Challenges in Nutrigenetics-Based Precision Nutrition

The rapid advancement of nutrigenomics within precision nutrition represents a significant shift in modern healthcare, transitioning from generalized dietary recommendations toward individualized interventions based on genetic profiles. Nutrigenetics, a core component of this paradigm, examines how genetic variation influences individual responses to nutrients, thereby enabling more targeted and potentially effective dietary strategies.³² However, beyond its scientific promise, nutrigenomics introduces complex ethical challenges that extend into the domains of privacy, justice, and

commercialization. The integration of genomic data with digital health technologies, coupled with the proliferation of direct-to-consumer (DTC) genetic testing, has transformed nutrigenomics into a field where ethical considerations are inseparable from technological innovation.^{5,33} Furthermore, the incorporation of artificial intelligence (AI) and large-scale data analytics intensifies these concerns, particularly regarding algorithmic bias and data governance.³⁴ These developments raise fundamental ethical questions about autonomy, fairness, and the responsible use of sensitive biological information.

Genetic data represent one of the most sensitive forms of personal information due to their predictive, permanent, and familial nature.⁵ Unlike conventional health data, genetic information can reveal long-term disease risks and extend beyond the individual to biological relatives, thereby complicating traditional frameworks of consent and confidentiality. From an ethical perspective, this raises significant concerns regarding autonomy. The increasing integration of genomic data into digital health ecosystems enhances both the utility and the vulnerability of such data.³² Genetic information is frequently stored, processed, and shared across multiple platforms, increasing the risk of unauthorized access and misuse. The integration of artificial intelligence (AI) further complicates this issue. AI systems rely on large datasets that may lack diversity, leading to biased outputs and inequitable recommendations.³⁴ This raises ethical concerns not only about privacy, but also about accountability and transparency in decision-making processes.

The rapid commercialization of nutrigenetic testing, particularly through DTC platforms, introduces significant ethical tensions between innovation and consumer protection.⁵ While increased accessibility may appear beneficial, it often occurs in the absence of sufficient regulatory oversight. A key ethical concern is the scientific validity of commercially available tests. Many nutrigenetic services rely on limited or inconclusive evidence and provide simplified dietary recommendations based on a small number of genetic variants.⁵ This raises concerns regarding nonmaleficence, as misleading or inaccurate information may result in inappropriate health decisions.

Furthermore, the commercialization of nutrigenomics involves the monetization of genetic data. Companies may collect, aggregate, and sell genetic information to third parties without transparent mechanisms for consent or benefit-sharing.³⁵ This raises fundamental ethical questions regarding ownership, fairness, and the exploitation of personal biological data. As highlighted by Phillips, DTC genetic testing is often marketed with minimal regulatory oversight, allowing companies to make claims that may not be fully supported by scientific evidence.²⁶ This further undermines informed consent and exposes consumers to potential harm. The integration of AI and digital platforms amplifies these concerns by enabling large-scale data extraction and commercialization.³⁴ Without appropriate governance, commercial interests may overshadow ethical considerations and public health priorities.

Across these domains, a central ethical tension emerges between technological innovation and the equitable distribution of its benefits. While nutrigenomics holds significant potential for improving health outcomes, its current implementation risks exacerbating existing inequalities.³² One major concern is the lack of diversity in genomic datasets, which limits the applicability of nutrigenetic findings across different populations.³³ AI-driven analyses based on nonrepresentative data may produce biased or ineffective recommendations, disproportionately affecting underrepresented groups.³⁴

Additionally, the digital divide plays a critical role in determining access to nutrigenetic services. Individuals with greater financial and technological resources are more likely to benefit, while disadvantaged populations may be excluded.²⁷ This creates the risk of “elite healthcare,” where personalized nutrition is accessible only to certain groups. Addressing these challenges requires ethical frameworks that prioritize equity, transparency, and accountability. Without such measures, the advancement of nutrigenomics may deepen, rather than reduce global health disparities.

Health Inequities in the Implementation of Nutrigenetics-Based Precision Nutrition

Nutrigenetic testing has been adopted to prevent various chronic diseases such as cardiovascular disease, cancer, diabetes, neurological disorders, and osteoporosis.³⁶ Despite its capacity to serve as an informative guide to individual health, a major issue that has appeared when developing modern medicine is the emergence of health disparities during its clinical implementation.^{36,37} Nutrigenetics-based interventions have been found to be much more successful than drug interventions alone in improving patient outcomes, according to previous studies.³⁸ The shifts from a common, population-level diet to individualized nutrition through nutrigenetics represent a significant innovation in healthcare. This approach is no longer dependent on “one size fits all” dietary recommendations, but allows for a nuanced consideration of the interaction among biology, behaviour, and environment.³⁹ However, as these multi-omics tools transition from the laboratory to clinical practice, they raise important equity concerns related to justice and human dignity.

Health is recognized as a fundamental human right that serves as the indispensable basis for human dignity and the subsequent right to food and specialized nutritional care.²⁷ Within the context of precision health, human dignity is closely linked to the “right to know” one’s biological health risks and to exercise autonomy in making informed health decisions.⁴⁰ This normative value requires that individuals are not treated merely as passive recipients of generalized, population-scale advice but are empowered through personalized detection to take proactive action to improve their specific health outcomes.⁴¹ However, truly respecting human dignity also means ensuring that the collection and processing of sensitive biological data do not impose unforeseen risks or burdens on individuals without their full understanding and explicit agreement.^{42,43}

The preservation of human dignity is fundamentally threatened when structural and economic barriers turn precision nutrition into a “boutique” service available only to the affluent, thereby creating an unjust and unequal distribution of the right to health.⁴⁴ From a bioethical perspective, justice and equality are essential pillars of dignity; therefore, a framework that offers “precision for some” while leaving marginalized groups with genetic or biologically inaccurate advice due to representational data bias violates these foundational human values.^{45,46} Protecting human dignity in the era of digital health necessitates inclusive design, robust regulatory oversight to prevent genetic discrimination, and the intentional removal of economic hurdles to ensure that the benefits of precision medicine promote the well-being of all citizens, regardless of their socioeconomic status or ancestral background.^{47,48}

Individuals identified as having genetic predispositions to certain conditions may face stigmatization or deterministic labelling, which can influence both self-perception and societal attitudes. This issue directly challenges the principle of justice. The potential misuse of genetic data in employment, insurance, or other institutional settings highlights the risk of unfair treatment based on biological characteristics.⁵ Although some legal protections exist, they are often limited and may not adequately address emerging applications of genetic data in digital and commercial contexts. Additionally, disparities in access to nutrigenetic services and genetic literacy further exacerbate these risks. Individuals with limited education or healthcare access may be more vulnerable to misinterpreting genetic information and less capable of protecting their rights.³⁵ This creates an ethical imbalance, where the benefits of nutrigenomics are not equitably distributed. Thus, while nutrigenomics aims to promote personalized health, it simultaneously risks reinforcing structural inequalities if ethical safeguards are not adequately implemented.

These barriers may result in inequitable access to personalized nutritional care, whereby only individuals with higher socioeconomic status can benefit from tools designed to identify and mitigate their health risks.²⁷ Geographic and infrastructure divides exacerbate these economic disparities even further. Currently, precision nutrition research and clinical implementation are primarily focused in urban academic medical centres in high-income countries (HICs), whereas rural populations and low- and middle-income countries (LMICs) suffer from severe telecommunications and diagnostic

gaps.^{27,49} High-speed internet, real-time data transmission, and wearable technologies such as continuous glucose monitors are often essential for precision nutrition. However, these resources may be inaccessible in regions with limited connectivity or underdeveloped regulatory infrastructure.^{49,50} In addition, a significant digital divide persists. Older adults and individuals with lower levels of education may have difficulty in navigating complex digital platforms or interpreting health information, limiting their ability to benefit from precision nutrition technologies even when such technologies are available.^{47,51} Another important threat to equity lies in the representational biases of scientific datasets used to train AI algorithms that support precision nutrition.

Currently, most genomic databases and models are derived predominantly from populations of European ancestry, limiting their applicability to other ethnic and ancestral groups. The genetic variability within an individual's ancestry may cause significant difference in nutritional processing. For example, a certain genotype may predict lactose intolerance in 85% of individuals of European ancestry, but only 42% among those of African descent.^{52,53} Similarly, the allele frequencies and effect sizes of variants in *TCF7L2*, a well-established genetic predictor of type 2 diabetes, differ substantially across European, Middle Eastern, and East Asian populations.³⁹ However, if predictive models are not trained on diverse datasets, they will inevitably give non-European populations inappropriate, ineffective or harmful dietary advice, leading to increased nutrition health inequalities.⁵³ The implications are exacerbated by social and structural determinants of health that transcend individual biology.

Best practices of nutrition may not be practical for marginalized populations living in low-quality food environments, dominated by ultra-processed food outlets and lacking of fresh, nutrient-dense staples. A careless disregard for cultural foodways and traditional dietary habits can cause precision interventions to be viewed as impractical or culturally inappropriate.^{37,54} Furthermore, without strong legal protections against genetic discrimination, such as those offered by Canada's Genetic Non-Discrimination Act, vulnerable populations may be uncomfortable to share sensitive biological information for fear of increased insurance premiums, workplace discrimination, or both.⁵⁵ Finally, a substantial workforce capacity gap remains; only 24% to 33% of registered dietitians feel comfortable incorporating nutrigenomics into their practice, with training frequently directed at elite institutions rather than safety-net clinics.⁵⁶ Addressing these multifactorial inequities is not merely a technical challenge but an ethical imperative to ensure that the benefits of precision nutrition enhance the health and dignity of all individuals, rather than becoming a privilege accessible only to a select few.

Conclusion

Nutrigenetics-based precision nutrition has the potential to transform dietary care by moving beyond generalized recommendations toward interventions tailored to individual genetic profiles. The evidence reviewed here demonstrates its clinical value across a range of applications, from management of metabolic disorders associated with variants in genes such as *FTO* and *MTHFR*, to micronutrient optimization and athletic performance. However, this scientific promise cannot be responsibly realized without confronting the ethical, legal, and social challenges that accompany its implementation.

In direct-to-consumer settings, informed consent often fails to ensure meaningful comprehension, as it is often reduced to a single digital agreement that obscures data privacy risks, pleiotropic implications of genes like the *APOE* variant, and the rights of vulnerable populations, including adolescents. Furthermore, equity-related challenges remain substantial. The high cost of testing, geographic disparities in infrastructure, the digital divide, and the underrepresentation of non-European populations in genomic training datasets all risk transforming precision nutrition into an exclusive privilege accessible primarily to already advantaged groups, while producing inaccurate or potentially harmful recommendations for others.

Addressing these challenges requires coordinated action across multiple fronts. Regulatory frameworks must be strengthened to enforce transparent and meaningful consent processes, establish binding standards for genetic data

governance, and require independent validation of commercial claims. Genomic literacy must be integrated into the training of dietitians, clinicians, and allied health professionals, given that fewer than one-third of practitioners feel confident applying nutrigenetic findings in clinical settings. Genomic databases must be expanded to include diverse ancestral populations so that AI-driven recommendations reflect the full breadth of human genetic diversity. Ultimately, the future of nutrigenetics-based precision nutrition will depend not only on scientific advances but also on the ethical and governance decisions made today. With sustained interdisciplinary commitment from scientists, clinicians, ethicists, policymakers, and the communities most affected, this field can evolve into a tool that advances health equity rather than undermines it.

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