OPEN ACCESS

COMMENTARY

The Innovation Nutrition

11-Oxygenated androgens: An underrecognized endocrine axis for precision nutrition research

Xianhua Zhang,[1,2,5,*] Huiyu Xu,[3,4,5,*] Jueyu Li,[1,2,5] Rong Li,[3,4,*] and Libo Zhao[1,2,*]

[1]Department of Pharmacy, Peking University Third Hospital, Beijing 100191, China

[2]Therapeutic Drug Monitoring and Clinical Toxicology Center for Peking University, Beijing 100191, China

[3]Center for Reproductive Medicine, Department of Obstetrics and Gynecology, Peking University Third Hospital, Beijing 100191, China

[4]National Clinical Research Center for Obstetrics and Gynecology, Peking University Third Hospital, Beijing 100191, China

[5]These authors contributed equally

*Correspondence: zhangxianhua432@163.com (X.Z.); huiyu56@bjmu.edu.cn (H.X.); roseli001@bjmu.edu.cn (R.L.); libozhao@bjmu.edu.cn (L.Z.)

Received: April 21, 2026; Accepted: June 12, 2026; Published Online: June 19, 2026; https://doi.org/10.59717/j.xinn-nutri.2026.100018

Citation: Zhang X., Xu H., Li J., et al. (2026). 11-Oxygenated androgens: An underrecognized endocrine axis for precision nutrition research. *The Innovation Nutrition* **1**:100018.

Understanding how nutrition shapes endocrine function remains a central challenge in metabolic and reproductive medicine. While insulin has long been considered a primary mediator linking dietary exposures to hormonal regulation, this paradigm may be incomplete. Dietary signals are increasingly viewed as being processed through interacting layers that include the gut microbiome, metabolite generation, and intracellular signaling pathways. This multi-layered architecture could influence endocrine outputs relevant to metabolic and reproductive phenotypes. Against this background, 11-oxygenated androgens (11-OAs) have emerged as a biologically and clinically relevant androgen pathway that may serve as an integrative endocrine readout of these interconnected processes.

ANDROGENS AT THE INTERFACE OF METABOLISM AND NUTRITION

11-Oxygenated androgens (11-OAs) are emerging as a clinically relevant androgen pathway that links adrenal steroidogenesis with insulin action, hepatic metabolism, and possibly host-microbiome interactions.[1-4] Yet they are still seldom discussed in nutritional endocrinology. Their immediate relevance to nutrition research is not that diet has already been shown to directly regulate this pathway, but that these steroids may capture biologically meaningful variation along a broader nutrition-microbiome-endocrine axis. In this axis, dietary exposures could be transformed by the gut microbiota into bioactive metabolites that may influence host metabolic and hormonal signaling.[1,4]

11-OAs enter nutrition research mainly because of where they sit in steroid biology. The adrenal gland is the main source of precursors, particularly 11β-hydroxyandrostenedione (11OHA4), which is converted in peripheral tissues to active androgens such as 11-ketotestosterone (11KT).[1] Importantly, 11KT has androgen receptor activity comparable to testosterone. This makes the pathway biologically relevant rather than a minor metabolic by-product, and places it at the intersection of adrenal output, peripheral conversion, insulin signaling, and tissue metabolism.[1]

The clearest human evidence for its clinical relevance comes from polycystic ovary syndrome (PCOS). Using liquid chromatography-tandem mass spectrometry (LC-MS/MS) profiling, O'Reilly and colleagues reported that 11-oxygenated C19 steroids are the predominant circulating androgens in PCOS, challenging the longstanding focus on testosterone alone.[5] This is relevant to nutrition science because PCOS is not only a reproductive endocrine disorder, but also a metabolic condition shaped by insulin resistance, adiposity, hepatic dysfunction, and marked phenotypic heterogeneity. In that setting, a steroid panel that reflects broader endocrine-metabolic biology may be more informative than a single conventional androgen measurement.[1,4-5]

At the same time, the present evidence should be interpreted cautiously. Current studies support 11-OAs as metabolism-sensitive endocrine markers, but do not yet demonstrate that specific diets, nutrients, or nutritional interventions directly and reproducibly regulate this steroid axis in humans. At present, their main translational value lies in phenotypic characterization rather than in established use as diet-responsive biomarkers.[1,3-4]

NUTRITION-MICROBIOME-INSULIN AXIS IN THE REGULATION OF 11-OXYGENATED ANDROGENS

One mechanistic entry point is insulin biology. Beyond serving as a metabolic signal, insulin may act as a bridge between nutritional exposures and androgen biology, particularly within the 11-OA pathway. Dietary patterns influence insulin dynamics, suggesting that nutrition could affect 11-OAs indirectly through insulin-mediated regulation of steroidogenesis. This evidence should be read as providing a practical basis for considering upstream nutritional and microbial modulators without implying direct dietary control of 11-OA production.

Beyond insulin-centered regulation, microbiome-derived metabolites may represent a second upstream layer of host signaling.[4] These metabolites can interact with intracellular signaling components and influence regulatory cascades.[1,4] In this conceptual model, this evidence should be read as support for a plausible upstream mechanism rather than as proof that the microbiome directly regulates circulating 11-OAs in humans.

From a nutritional perspective, dietary patterns are known to differ in their effects on insulin exposure and metabolic context. By extension, such insulin-driven differences could plausibly modulate the 11-OA axis, but

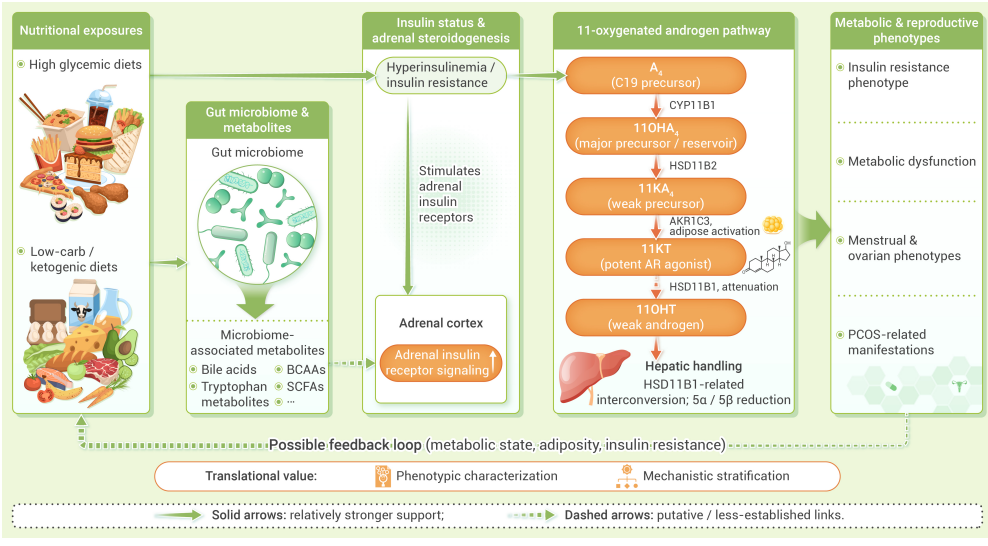

Figure 1. Proposed nutrition–microbiome–insulin framework for 11-oxygenated androgen regulation
Nutritional exposures may influence insulin status and microbiome-associated metabolites, which may converge on adrenal steroidogenesis and 11-oxygenated androgen metabolism. The resulting 11-OA profile may support phenotypic characterization and mechanistic stratification. Solid arrows indicate better-supported relationships; dashed arrows indicate putative links.

direct 11-OA-specific dietary evidence remains limited.

Supporting this framework, interventional studies targeting insulin resistance have shown that metabolic interventions can reshape androgen profiles. Weight loss and physical activity improve insulin sensitivity and are often associated with reductions in circulating androgens. Similarly, insulin-sensitizing therapies such as metformin or glucagon-like peptide-1 (GLP-1) receptor agonists have been shown to modify steroid hormone profiles in metabolic and reproductive disorders. Because most of these data concern conventional androgens rather than 11-OAs, they should be viewed as indirect support for insulin as an upstream regulator of steroidogenesis.

Walzer *et al.* reported marked elevations of adrenal-derived 11-OAs in women with severe insulin resistance, supporting a role for adrenal insulin receptor signaling in their regulation.[2] This observation is highly relevant to nutrition research, as insulin exposure and sensitivity are primary targets of dietary, weight-loss, and exercise interventions. If 11-OAs are insulin-sensitive steroids, nutritional interventions that modify insulin biology could plausibly influence this pathway, although this possibility still requires direct testing.

IMPLICATIONS FOR PRECISION NUTRITION AND TRANSLATIONAL RESEARCH

The liver provides another relevant layer. McDonnell and colleagues showed substantial hepatic metabolism of 11-OAs in humans using integrated *in-vivo* and *ex-vivo* approaches, indicating that the liver actively transforms these steroids rather than simply clearing them.[3] Many nutritional exposures act through hepatic lipid handling, gluconeogenesis, inflammation, and redox biology. An androgen pathway that is metabolically active in the liver and linked to systemic insulin physiology may therefore provide a useful readout of broader metabolic state.[3]

This hepatic aspect also matters for biomarker development. Nutrition studies need endocrine markers that are analytically reliable, biologically informative, and interpretable across metabolic contexts. Because 11-OAs reflect adrenal output, peripheral activation, and hepatic handling, they may provide a more integrated endocrine signal of metabolic state than isolated measurements of classic androgens alone.[1,3]

Implications for precision nutrition should currently be framed as study-design opportunities rather than clinical dietary advice. In future trials, baseline or longitudinal 11-OA profiles could be evaluated as stratification variables to distinguish responders and non-responders to energy restriction, low-glycemic-index, low-carbohydrate/ketogenic, or insulin-sensitizing interventions. Their value would likely be greatest when integrated with metabolomics, microbiome profiling, liver function, body composition, insulin action, and reproductive phenotype. Such multimodal profiling could help identify obesity, PCOS, nonalcoholic fatty liver disease (NAFLD)/metabolic-syndrome, or severe insulin-resistant subgroups in which androgen biology is more tightly coupled to nutritional or metabolic intervention response.

Analytical methodology is central to translation rather than a mere technical detail. Advances in this field have relied on LC-MS/MS for accurate profiling of structurally related, low-abundance steroids. In PCOS and related metabolic-reproductive settings, such profiles may help refine phenotypes, whereas expanded androgen panels are better suited for subtype characterization than initial triage.[1,4-5]

However, LC-MS/MS-based 11-OA profiling also has important methodological limitations. Cross-study interpretation requires attention to pre-analytical variables, including sample matrix, collection timing, menstrual or reproductive status, storage conditions, and freeze-thaw history, as well as sample preparation, derivatization strategy, matrix effects, calibration, commutable quality-control materials, reference intervals, and inter-laboratory agreement. Cost, instrument availability, and specialist expertise may also limit accessibility outside reference laboratories. Without greater assay standardization and external comparability, 11-OA measurements should be used cautiously in multicenter nutrition studies and should not yet be treated as routine clinical nutrition tests.

This microbiome layer remains speculative but biologically interesting. Host-microbial co-metabolism and microbiome-associated signaling could in principle influence steroid-related substrate pools or host endocrine-metabolic regulation feeding 11-OA pathways. Whether such mechanisms meaningfully alter circulating 11-OAs in human metabolic disease remains unproven, but they offer a plausible conceptual link between endocrine metabolism and nutrition-related microbial ecology.[4]

For nutrition research, the main value of 11-OAs is therefore not immediate clinical application but added biological detail. In settings such as PCOS, obesity, NAFLD/metabolic syndrome, or severe insulin resistance, they may help separate endocrine patterns that are flattened when only conventional androgens are measured.[1-5]

As illustrated in Figure 1, the proposed framework starts with nutritional exposures and the gut microbiome/metabolite layer, moves through insulin dynamics and adrenal steroidogenesis, and then incorporates hepatic steroid handling and peripheral conversion before reaching metabolic and reproductive phenotypes. Solid arrows represent relationships with relatively stronger supporting evidence, such as insulin resistance and androgen biology or hepatic 11-OA metabolism. Dashed arrows represent putative links that require validation, including microbiome-mediated steroid metabolism and feedback from downstream metabolic states to the broader nutritional context.

FUTURE DIRECTIONS AND EVIDENCE BOUNDARIES

The field now needs less cross-sectional description and more longitudinal and intervention-based evidence. Useful next steps include tracking 11-OAs during weight loss or metabolic deterioration; testing low-glycemic-index, energy-restriction, lower-carbohydrate/ketogenic, or insulin-sensitizing interventions; and integrating steroid profiles with liver function, body composition, microbiome features, metabolomics, sex- and age-related variation, and reproductive phenotype. Repeated-measures designs may be particularly helpful because they can separate relatively stable endocrine patterns from short-term biological fluctuations better than a single baseline sample.[1,3-4]

For the time being, 11-OAs are best viewed not as obscure steroid by-products but as part of a metabolically relevant endocrine pathway. Their current value lies in mechanistic phenotyping and translational stratification rather than in routine nutritional screening, and that promise still needs to be tested in longitudinal and intervention studies.[1-5]

In summary, 11-OAs should be considered candidate metabolism-sensitive endocrine readouts rather than proven nutrition-responsive biomarkers. Microbiome-derived metabolites can act as host-signaling regulators in other contexts, but whether such pathways materially regulate circulating 11-OAs in humans remains to be validated. Within this proposed framework, 11-OAs may serve as markers of adrenal activity and as candidate downstream readouts of integrated nutritional, microbial, hepatic, and metabolic regulation.

DECLARATION OF GENERATIVE AI AND AI-ASSISTED TECHNOLOGIES IN THE WRITING PROCESS

During the preparation of this work, the authors used ChatGPT for language editing, structural revision suggestions, and editorial polishing. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

REFERENCES

1. Turcu A. F., Rege J., Auchus R.J., et al. (2020). 11-oxygenated androgens in health and disease. *Nat. Rev. Endocrinol.* **16**:284–296. DOI:10.1038/s41574-020-0336-x
2. Walzer D., Turcu A. F., Jha S., et al. (2022). Excess 11-oxygenated androgens in women with severe insulin resistance are mediated by adrenal insulin receptor signaling. *J. Clin. Endocrinol. Metab.* **107**:2626–2635. DOI:10.1210/clinem/dgac365
3. McDonnell T., Anthony A. V., Clarke G., et al. (2025). Hepatic metabolism of 11-oxygenated androgens in humans: An integrated in vivo and ex vivo approach. *Eur. J. Endocrinol.* **193**:340–347. DOI:10.1093/ejendo/lvaf166
4. Xu H., Zhang H., Yang R., et al. (2026). From testosterone to 11-oxygenated androgens: Integrating endocrine biology, nutrition, and systemic health across the lifespan. *Innov. Nutri.* **1**:100004. DOI:10.59717/j.xinn-nutri.2026.100004
5. O'Reilly M. W., Kempegowda P., Jenkinson C., et al. (2017). 11-oxygenated C19 steroids are the predominant androgens in polycystic ovary syndrome. *J. Clin. Endocrinol. Metab.* **102**:840–848. DOI:10.1210/jc.2016-3285

FUNDING AND ACKNOWLEDGMENTS

This work was supported by the National Natural Science Foundation of China (Grant No. 82172368). The funder had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.