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Review

Pattern recognition receptors as potential therapeutic targets in metabolic syndrome: From bench to bedside

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ABSTRACT

Pattern recognition receptors (PRRs) such as Toll-like receptors (TLRs) and NOD-like receptors (NLRs) play crucial roles in the underlying mechanisms of metabolic syndrome (MetS). Mainly, these receptors have been suggested to participate in the pathophysiological processes involved in the complications associated with this condition. Therefore, to evolve therapeutic strategies targeting PRRs might be an imperative approach to avoid the development of further complications in human subjects. In this work, we discuss the understanding regarding the roles of PRRs in the pathways of MetS to further describe potential advancements made to target these receptors within this pathology.

1. Introduction

Metabolic syndrome (MetS) is a significant contributor to the development of cardiovascular diseases (CVDs), especially in adults (>18 years or older) [1]. This disease affects approximately 34% of individuals in this age range within the United States [2]. To clarify the interplay between MetS and cardiovascular complications, it is essential to consider the various risk factors encompassing this pathology such as hyperglycemia/insulin resistance, high blood pressure, dyslipidemia, and, especially, abdominal obesity (Table 1) [3]. These risk factors are markers for the development of MetS, and potentially CVDs [1,3].

Abdominal obesity is suggested to be one of the most important metabolic indicators associated with MetS according to previous studies [4,5]. It has been estimated that 71.6% of adults in the United States are overweight and 39.8% are obese [6]. Indeed, it is clear that inflammatory mechanisms are present in abdominal obesity [7], and inflammation is one of the critical mechanisms found in MetS patients [8,9]. Notably, it indicates that an immune response has been initiated in the body triggered possibly by activation of pattern recognition receptors (PRRs) [8]. PRRs, located in innate immune and non-professional immune cells, are responsible for detecting foreign pathogens within the body [10]. These receptors also drive the recognition of signals and/or cell molecules associated with cellular stress and damage in chronic pathologies [10], such as MetS [8,11].

Many types of PRRs are crucial for mediating the innate immune response [10]. Two of the most common classes of receptors involved in metabolic risk factors are Toll-like receptors (TLRs) and NOD-like receptors (NLRs) [8], which are transmembrane and cytoplasmic receptors, respectively [10]. Once activated these receptors initiate signaling cascades that lead to the inflammatory response associated with many of the risk factors in MetS [8]. Then, important cell signaling proteins like NF-κB and mitogen-activated protein kinases (MAPKs) as well as the inflammasome complex are activated [8,11]. Therefore, targeting these receptors might be a powerful strategy for managing the complications associated with MetS. This review will discuss the new developments being made in understanding the relationship between PRRs and MetS as well as the implications of therapeutic targeting these receptors for controlling the complications associated with MetS.

2. PRRs in MetS: signaling pathways

In humans, several recognition systems have evolved to sense exogenous and endogenous ligands [12]. PRRs, found in the cell membrane or cytoplasm of a cell, are integral components of these recognition systems. Studies suggest that exogenous and endogenous ligands such as PAMPs and DAMPs (pathogen and damage-associated molecular patterns, respectively) are recognized through activation of these receptors [10]. The mechanisms of MetS

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Table 1
Risk factor parameters for the diagnostic of MetS.

Risk factor	Defining level
Abdominal obesity	>40 and > 35 inches for men and women, respectively
Triglycerides	≥150 mg/dl
HDL cholesterol	<40 and < 50 mg/dl for men and women, respectively
Blood pressure	≥130/85 mmHg
Fasting glucose	≥100 mg/dl

Extracted from Grundy et al., 2004 [1] and adapted with current guidelines from the American Heart Association (www.heart.org).

include many PRRs. However, TLRs and NLRs are the most well characterized in this pathology [8]. As of recent, there are limited studies focusing on the role of these receptors in MetS in humans. Therefore, the studies discussed in this work were mainly conducted with murine animals. It has been suggested that most ligands involved in the mechanisms of MetS have the potential to initiate the innate immune process [8,13]. Still, it is not well-known which ligands are responsible for these receptors activation, or the mechanisms by which they execute this process.

TLRs are integral membrane proteins that contain: a leucine-rich repeat (LRR) domain for ligand identification, a transmembrane helix, and a carboxy-terminal intracellular signaling domain [14]. These receptors are found in the cell membrane except for TLR3, TLR7, TLR8, and TLR9 which are present in the endosome [14]. Apart from mediating the innate immunity, TLRs are also involved in the inflammatory pathways associated with MetS [8,15]. After their activation, TLRs enlist adaptor proteins through the MyD88-dependent pathway and MyD88-independent pathway (TRIF-dependent) [16]. TLR3 is the only TLR to solely signal through the MyD88-independent pathway, and TLR4 is known for signaling using both downstream pathways [16]. Early activation of NF-κB and MAPKs stimulation might be regulated by TLRs via the MyD88-dependent pathway [17]. Conversely, the MyD88-independent pathway triggers late-phase activation of NF-κB and production of type I interferons [17].

In humans, NLRs are chief protein receptors located in the cytoplasm playing crucial roles in innate and adaptive immunity [18]. There are twenty-two different human NLR genes [18,19]. These receptors have a central NOD (NACHT: NAIP, CIITA, HET-E, and TP-2), a stretch of carboxyl-terminal LRR motifs, and the effector domain in N-terminal [19] and are classified by their function in inflammasome assembly, signaling transduction, transcription activation, and autophagy [20]. For this review, we will only focus on the pathways of NOD1, NOD2, and NLRP3 as they are the most well investigated NLRs in the mechanisms associated with MetS [8]. It has been observed that both NOD1 and NOD2 receptors lead to NF-kB stimulation and increased MAPK activity [20,21]. The NLRP3 protein is responsible for recognizing metabolic stress and aiding in the assembly of a multimeric protein complex known as the inflammasome [22]. Notice that this complex might also be activated by other NLRs (See Ref. [23] for review). This inflammasome, upon formation, leads to the activation of caspase-1 and the release of inflammatory cytokines (e.g., IL1β and IL-18) [22].Whereas the proteins recruited or activated by TLRs and NLRs following stimulations by PAMPs or DAMPs are very divergent, the utmost triggered mechanisms are similar and involve secretion of inflammatory mediators as well as increased oxidative stress, which contribute to the pathophysiology of the risk factors associated with MetS [7–9].

3. The crosstalk between PRRs and the pathophysiology of MetS

To understand the interaction between PRRs and the pathophysiology of MetS (Fig. 1), it is important to investigate the pathways involved in innate immunity. Abnormal innate immunity activation (TLRs and NLRs), by PAMPs and/or DAMPs, contributes to the pathological processes of this cluster of diseases and helps bridge the relationship between inflammation and metabolic disorders [5,7,8]. The release of pro-inflammatory cytokines via the NF-κB signaling pathway is controlled by TLRs and NLRs [24]. Furthermore, the NF-κB pathway might stimulate the production of multiple anti-apoptotic factors, chemokines, and adhesion molecules [24]. Therefore, inflammation might be recognized not only as an indicator but also as a relevant risk factor for numerous pathologies and recent evidence suggests that PRRs (TLRs and NLRs) may have a considerable role in the recruitment and activation of these molecules [25,26].

In a pioneer work, Edfeldt and collaborators [27] revealed that out of 9 human TLRs, TLR1, TLR2, and TLR4 levels are the most prominent in human atherosclerotic lesions having implications in plaque formation. Other studies have shown that TLR7 levels are upregulated in human adipose tissue [28] and that TLR3 deficiency in mice affects triglycerides metabolism as well as glycemic control [29]. Indeed, TLR3 loss of function improves glucose tolerance while reducing liver steatosis in a murine model of obesity [30]. In addition, other TLRs such as TLR6 and TLR8 have also been suggested to contribute to the mechanisms of MetS as follows: TLR6 was shown to be elevated in hepatocytes of obese patients with non-alcoholic fatty liver disease (NAFLD) [31] and TLR8 levels are increased in obese type 2 diabetic patients [32].

The TLRs 2 and 4 have been highlighted as essential mediators of insulin resistance, which comprises the core of MetS [8]. Indeed, TLR2 deficiency protects mice fed with a high-fat diet against obesity and adipocyte hypertrophy. These animals also have improved insulin sensitivity and reduced expression of the extracellular-signal-regulated kinase 1/2 (ERK1/2) [33]. Likewise, deletion of TLR2 in mice prevents against hypercholesterolemia, hepatic steatosis [34], and beta-cell dysfunction [35]. Regarding TLR4, its modulation in MetS occurs partly through saturated fatty acids [36,37]. This receptor has been extensively demonstrated to contribute to the development of obesity, insulin resistance, and vessel inflammation [37]. However, tissue-specific knockdown of TLR4 led to contradictory finds. In the arcuate nucleus of the hypothalamus TLR4 deficiency prevents against obesity-related metabolic disorders [38] whereas deletion of TLR4 in the intestinal epithelium augments MetS [39]. More importantly, both TLR2

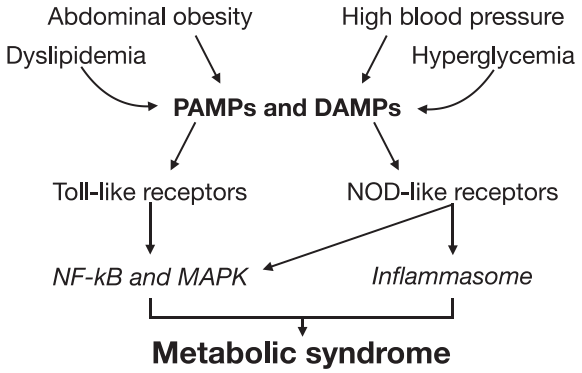

Fig. 1. Overview of pattern recognition receptors (PRRs) in the pathophysiology of metabolic syndrome (MetS). The risk factors for MetS generate pathogen and damage-associated molecular patterns (PAMPs and DAMPs, respectively) that activate PRRs such as Toll-like receptors and NOD-like receptors. Stimulation of these receptors affect the expression of the transcriptional factor nuclear factor-κB and MAPKs as well as the assembly of the inflammasome, which together contributes to the pathophysiological mechanisms of MetS.

and TLR4 mRNA levels are increased in human monocytes under MetS [25], therefore pharmacologically targeting their pathways might be of interest for emerging therapeutic strategies to treat the complications of this condition.

TLR5 and TLR9 have also been suggested to participate in MetS, but their roles are not yet fully understood. Regarding TLR5, its deletion in mice has been shown to alter the gut microbiota and lead to hyperlipidemia, hypertension, insulin resistance, and increased adiposity [40]. Conversely, another group showed that only TLR5 knockout does not determine the gut microbial composition and that environmental factors might play a role in the mechanisms leading to MetS [41]. Concerning TLR9, Hong and collaborators have demonstrated that its deletion increases body weight, impairs glucose tolerance as well as insulin resistance, and elevates secretion of pro-inflammatory cytokines [42]. However, Nishimoto and collaborators showed that TLR9 knockout or its pharmacological blockade improves insulin sensitivity and reduces macrophage accumulation in adipose tissue [43]. Noteworthy, it is acceptable that complete gene deletion or knockdown in animals may cause unexpected physiological adaptations and counter interactions between signaling pathways due to compensatory mechanisms.

As of recently, more information has surfaced on the role of TLR10 and the influence that it might have in biological systems. This receptor was shown to have anti-inflammatory properties by promoting the production of 1L-1Ra [44]. The anti-inflammatory properties of TLR10 might also be due to its dimeric capabilities, allowing it to interact with other TLRs and influence their signaling pathways [45]. It was also suggested that TLR10 demonstrates increased expression in the adipose tissue of both obese and type 2 diabetic individuals in the presence of ROS [46]. Furthermore, TLR10 was proposed to affect adipose tissue morphology in obesity [45].

About NOD1 and NOD2 receptors, the literature shows that their double knockout protects mice fed with a high-fat diet against inflammation, lipid accumulation, and peripheral insulin resistance [26]. However, while the NOD1 receptor has been found to be increased in subcutaneous adipose tissue from patients with MetS, NOD2 levels were not significantly different between MetS patients and matched controls. In this group of patients, authors also observed that the downstream mediators RIP2 and NF- κB, as well as the cytokine profile, were remarkably higher [47]. Indeed, human adipocytes stimulated with iE-DAP (specific ligand for NOD1) presented decreased insulin signal transduction linked to elevated c-Jun N-terminal *kinase (*JNK) and impaired insulin receptor substrate 1 phosphorylation [48].

The chief contribution to MetS complications arising from the inflammasome is the conversion of pro-inflammatory cytokines (pro-IL-1b and pro-IL-18) into their bioactive forms [22]. Recent evidence suggests that inflammatory cytokines contribute to damage, even in small quantities, and that boosts in their production lead to increase in mediators of oxidative stress [49]. Also, inflammasome assembly triggers pyroptosis, which is a caspase-1 induced cell death characterized by higher levels of inflammation [50]. This process releases a variety of DAMPs into the extracellular environment. Thus, it might be a mechanism that enhances inflammation *via* a positive feedback loop.

As mentioned before, MetS drives an intensification in reactive oxygen species (ROS) generation and, consequently, oxidative stress [51]. Diet-induced obesity triggers the release of ROS in different generating enzymes through a large number of mechanisms [52]. Briefly, free radicals might be produced by the nicotinamide adenine dinucleotide phosphate oxidase (NADPH-oxidase) enzyme under MetS [53], and TLR4 was previously demonstrated to modulate this enzyme [54]. Also, ROS might be recognized by NLRP3, which stimulates the assembly of the inflammasome [22]. Another interesting point here is the fact that crosstalk occurs between ROS and NF-kB [55]. Although the exact nature of this process remains unclear, it has been shown that ROS can influence NF-kB nuclear translocation through different signaling pathways and that NF-kB may control ROS production at the molecular level [55]. Additionally, both ROS and TLR4 affect the concentrations of the vasoprotective molecule, nitric oxide (NO) [56,57].

Evidence that PRRs (TLRs and NLRs) participate in the pathophysiological mechanisms of MetS are pointed out in this review. The network of signaling pathways that are stimulated by these receptors involves overlapping mechanisms and crosstalk interactions that might be highlighted as potential pharmacological targets to treat complications associated with MetS.

4. PRRs and gene polymorphisms in MetS

PRRs, such as the ones involved in the pathophysiology of MetS, have been suggested to be modified by gene polymorphisms [58,59]. Thus, creating variations that might have implications in their functional activities. While occurrence and outcomes linked to gene polymorphisms in humans are still unclear, uncovering their patterns might be a promising approach for detecting potential risk factors for the progression of MetS as well as CVDs.

Although the TLR2 (R753Q) and TLR4 (D299G and TLR4/T399I) genetic variations were shown to be unrelated with type 2 diabetes, this gene polymorphism in TLR2 was associated with lower levels of HDL in a population in Mexico [60]. It is important to understand that different variations might lead to divergent fallouts. For example, in the Chinese Han population was identified that some changes in the TLR4 gene increase the risk for developing type 2 diabetes [61]. In another study, it was demonstrated that presence of more than one copy of a specific haplotype SNP in the TLR2 gene, known as TLR2-Ht4, may have the ability to protect against diabetes [62]. It was also reported that the SNP1350 T/C might protect against acute myocardial infarction and arterial hypertension whereas the TLR4 SNP896 A/G polymorphism does not correlate with these conditions [63].

As previously discussed, obesity is a central point in the development of MetS. Indeed, preventing the inflammatory process associated with visceral fat is a key mechanism for precluding related complications in this pathology. The D299G/T399I TLR4 polymorphism was shown to be correlated with augmented body fat and to insulin resistance [64], a core component in the pathways of MetS. Analogously, the TLR2 rs5743708 variant is associated with morbid obesity [65], a far more serious condition for the pathogenesis of MetS. Regarding TLR5, it was shown that the nonsense polymorphism (R392X) predisposes to type 2 diabetes while protecting against obesity [66], which is an interesting finding, especially because obesity is a known risk factor for type 2 diabetes. Interesting, loss-of-function variations in TLR10 associated with SNPs enhance the production of cytokines *via* TLR2 [44] promoting inflammation and overpowering disease in affected patients.

Similarly to the results observed with TLRs, gene polymorphism in NLRs also produce distinct patterns depending on the variation and receptor affected. The NLRP3 rs10754558 variation was shown to be associated with the presence of type 1 diabetes in a pediatric group from Northeast Brazilian [67] and with the development of type 2 diabetes in a study conducted in a hospital in China [68]. However, other variations such as rs5112998 and rs12137901 were shown to be unrelated to susceptibility to diabetes [68]. In the case of the NOD2 receptor, for example, the presence of specifics haplotypes in its locus might be associated with coronary heart disease in pre-hypertensive patients [69].

In summary, gene polymorphisms in PRRs such as TLRs and NLRs may lead to different outcomes in healthy and diseased conditions such as MetS. Still, understanding the correlation between gene polymorphisms in PRRs and metabolic risk factors might provide a novel diagnostic tool in genome-wide association studies.

5. Therapeutic strategies targeting PRRs in MetS

Considering the emerging role allegedly played by PRRs in the pathophysiology of sterile inflammation, it is not surprising that these receptors and/or their downstream signaling pathways have been the object of attention in multiple studies. Although there is an indication of benefits for addressing these receptors in chronic diseases, we are only now enlightening potential therapeutic targets (see Table 2 for references). In this section, we consider preliminary data from ongoing and completed clinical trials registered in the United States connecting risk factors for MetS to the pathways of innate immunity.

The most prominent drug used to target TLR4 pathways, eritoran tetrasodium, has been used to investigate the effects of this receptor inhibition in two clinical trials. First, eritoran was tested in a randomized control trial with 60 adults of both genders. The main goal of the authors was to determine whether pharmacological blockade of TLR4 with this compound reduces inflammation and improves glucose tolerance in obese type 2 diabetic patients (NCT02267317). The same research group went on in another experiment aiming at determining if TLR4 plays a role in lipid-induced insulin resistance in lean, non-glucose tolerant patients (NCT02321111). In both cases, the studies were suspended in Phase 2, and according to the NIH website (clinicaltrials.gov), this happened because the drug has expired and it is pending availability from the supplier.

Further analyzing the literature, it was observed that lean individuals injected with a non-esterified fatty acid presented an increase in TLR4 expression and TLR4-driven signaling, which has severe implications in insulin resistance in humans (NCT01740817). In another randomized controlled trial, 42 children with type 1 diabetes and hypercholesterolemia were treated with Atorvastatin (NCT01236365). The drug lowered LDL-C, apoB, and atherogenic lipoprotein sub-particles without worsening insulin resistance [70]. These results are of interest, mainly because statins have been shown to reduce TLR4 activation in animal models [71,72]. Additionally, statins are Food and Drug Administration (FDA) approved drugs for lowering LDL cholesterol (www.fda.gov). Therefore, this class of drugs is a potential candidate for repurposing in MetS. In line with this study, another randomized trial (NCT01420328) evaluated the effects of the drug Vytorin® (ezetimibe and simvastatin) in obese subjects. The drug suppressed TLR2 and TLR4 expression levels exerting anti-inflammatory effects [73].

Regarding the inflammasome, two interventional studies have been conducted. In the first one, authors tested whether fasting reduces the activation of NLRP3 (NCT02122575), they observed that this intervention might be a novel approach to reduce circulating levels of saturated fatty acids. In a prospective cohort study analyzing the effects of fasting and refeeding on T-cell fate (NCT02719899), a previous research reported that it appears that caloric restriction reduces the incidence of atherosclerosis [74]. Nevertheless, it is still not clear how this process happens and the clinical applicability of this alternative intervention.

Besides clinical trials, these receptors have been extensively studied in basic research, which uses antibodies and small molecules as well as repurposing drugs. TLR4 when targeted with SPA4, a peptide that binds surfactant A and antagonizes this receptor, in cultured cells decreased NF-kB nuclear translocation and, for consequence, secretion of the pro-inflammatory cytokine (TNF-alpha). The cyclohexene inhibitor TAK-242 (also known as CLI-095 or resatorvid), which binds the TIR domain of TLR4 and blocks the recruitment of protein adaptors (MyD88 and TRIF), prevents high blood pressure, reduces cardiac and renal fibrosis, decreases oxidative stress as well as phospho-JNK1/2 and NF-kB in animal models [75–77].

To date, no therapeutic intervention directly targeting the inflammasome has been established. Most of the studies targeting this complex involve pharmacological molecules to antagonize or block downstream effectors such as anakinra, rilonacept, and XOMA 052 [22]. The drug anakinra, which is an IL-1 receptor antagonist, when used in a model of diabetes (streptozotocin-induced diabetic rats) improved endothelial function by not only blocking the effects of IL-1, but also by reducing NADPH-oxidase activity, NF-kB translocation, and the enzymes COX and iNOS [78]. Therefore, it appears that it might be a potential pharmacological agent for treating complications associated with MetS.

The NOD1 receptor has also been addressed through small

Table 2
Clinical trials targeting PRRs conducted in the United States with potential clinical relevance to the management of MetS.

Trial number	Project description/title	Main outcomes
NCT02267317	To determine the effect of TLR4 inhibition in obese and type 2 diabetic subjects	Suspended in phase II
NCT02321111	To assess the role of TLR4 in lipid-induced insulin resistance	Suspended in phase II
NCT01740817	To determine the effect of lipid infusion on TLR4 signaling	A sustained, mild elevation in plasma non-esterified fatty acid is sufficient to increase TLR expression and TLR-driven signaling in lean individuals
NCT01151605	To understand the possible beneficial effects of insulin in inflammation.	Unknown
NCT01236365	Statin in children with T1D and hypercholesterolemia	Atorvastatin lowered LDL-C, apoB, and atherogenic lipoprotein sub-particles without worsening insulin resistance
NCT02781350	Anti-inflammatory effects of fiber	Unknown
NCT01420328	The impact of Vytorin® on intracellular lipid and inflammation in obese subjects	The Vytorin® drug inhibits and reverses the pro-inflammatory and pro-atherogenic effects of dairy cream in obese patients
NCT00931879	Lovaza® and microvascular function in type 2 diabetes	Unknown
NCT02122575	To evaluate the effects of fasting on the NLRP3 inflammasome	Twenty-four hours fasting reduces NLRP3 inflammasome activation in healthy subjects
NCT02719899	Effect of fasting and refeeding in T-cell fate	It appears that long-term caloric restriction reduces pro-inflammatory mediators and the risk for atherosclerosis

Data extracted from the clinicaltrials.gov website. PRRs: pattern recognition receptors; MetS: metabolic syndrome; TLR: Toll-like receptor; NF-kB: nuclear factor kappa-light-chain-enhancer of activated B cells; MAPKs: mitogen-activated protein kinases; LDL-C: low-density lipoprotein C; apoB: apolipoprotein B; T1D: type 1 diabetes; NLRP3: nucleotide-binding oligomerization domain-like receptor protein 3.

molecules such as Noditinib 1 or GSK'217 [79]. Additionally, the downstream effector RIP1 might be targeted with the particular inhibitor GSK'214. Although these inhibitors might block NOD1-induced pathophysiological effects, their implications for MetS are yet-to-be-defined. Regarding TLR9, it has been reported that lysosomotropic chloroquine impairs its signaling and therefore protects against blood pressure elevations in spontaneously hypertensive rats (SHR) [80]. Hypertension is a comorbidity of MetS that appears to be tightly linked to TLRs pathways, not only through TLR9 but also through TLR4 downstream pathways [13].

Altogether, it is becoming clear that targeting PRRs whether for managing associated complications in MetS or other conditions might be an alternative in cases for which the available drugs are not effective. However, even though, we presented evidence in this work that these receptors play critical roles in the pathways of MetS, we still have a long path to uncover the precise molecular modulators in order to avoid unexpected side-effects as well as complete immunosuppression.

6. Final remarks

Throughout the literature, we observed that the PRRs (TLRs and NLRs) discussed in this work participate in the pathophysiological mechanisms associated with the risk factors of MetS. The receptors and mechanisms involved in these signaling pathways influence different crosstalk interactions, and might act as potential pharmacological targets to treat complications associated with this condition. It appears that activation of PRRs results not only in (pro)-inflammatory cytokines secretion but also in increased oxidative stress, which together impairs homeostasis aggravating the pathophysiology of MetS. Therefore, target these receptors might be a novel strategy within the intricate pathways underlying MetS.

Therapeutic manipulation of PRRs was previously acclaimed as an exciting approach to manage chronic diseases. However, it is essential to consider that targeting innate immunity can cause unforeseen consequences, mainly because these receptors are the first line of defense in humans against pathogens and they are also responsible for triggering the adaptive immunity. In this case, an utmost question that remains unanswered is whether the use of immunomodulators would produce better outcomes for MetS patients when matched to the standard pharmacotherapy which includes FDA approved drugs for isolated risk factors. At this point, one could speculate that this approach might be useful for treating patients that do not respond to treatment with available drugs.

Author agreement/declaration

All authors have seen and approved the final version of the manuscript being submitted.

Conflicts of interest

The authors declare no competing interests.

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