Expression of Toll-Like receptors in metabolic syndrome: A systematic review

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Abstract

Introduction: Toll-Like Receptors (TLRs) of innate immune system have documented roles in the pathogenesis of metabolic disorders. This study aims to systematically review the expression of TLRs on metabolic syndrome (MetS).

Materials and methods: We systematically searched PubMed/Medline, ISI web of Science, Scopus, Google Scholar, EMBASE, and OVID databases until February 2017. The terms ''Metabolic Syndrome'' OR ''Mets'' AND ''Toll like receptor'' OR ''Toll like'' OR ''TLRs'' OR ''TLR'' were used. "Expression" advertently was not used in our search and was considered in the selection process. Three steps for selecting the articles and then their qualification were conducted.

Results:

First, 1373 articles were found in the international databases. After removing duplicates, 963 papers remained and after two steps of selection, this number reached 410 and then 27, respectively. After full text screening and qualifying processes, we finally included 13 articles consisting of five animal and eight human studies. All human studies reported overexpression of TLRs (types 2, 4, 5, 9) in MetS, and most animal studies documented an increased TLRs expression.

Conclusion: This systematic review provides evidence for the relation of innate immune system with MetS. Its findings regarding overexpression of special TLRs (e.g. types 2, 4, 5, 9) in MetS and their basic mechanisms and clinical implications might be investigated in further studies.

Keywords: Metabolic Syndrome, Toll-Like Receptors, Chronic disease, Inflammation

Introduction

Metabolic syndrome (MetS) is defined as coincidence of metabolic disorders including dyslipidemia, abdominal obesity, hypertension and insulin resistance/glucose intolerance (1). It has emerged as a worldwide epidemic and major public health care concern with an increasing prevalence rate (2). In addition to its high prevalence rate, the importance of MetS is because of its association with worldwide

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epidemics of diabetes, cardiovascular diseases and nonalcoholic fatty liver disease (NAFLD) (3, 4). Many studies have proposed that conditions as MetS, atherosclerotic cardiovascular disease, insulin resistance, and obesity are associated with the activation of innate immune system. Latest evidence suggests that much of this association can be traced to a unique family of pattern recognition receptors known as Toll-Like receptors (TLRs) (5-8).

TLRs are trans-membrane receptors that are widely expressed in immune, epithelial and endothelial cells. Most of these receptors are on the cell surface, except for TLR 3, -7, -8, and -9, which mainly are in the endosomes and lysosomes (9). Briefly, TLR activation promotes inflammatory signaling cascade, phagocytosis, oxidative burst and eventually insulin resistance (10, 11). Important agonists that trigger TLR activity are saturated fatty acids, endotoxins, oxidized LDL, and damage-associated molecular patterns (12-14). It is suggested that targeting the TLRs pathway may be an effective method to help treating these disorders (15).

Large body of evidence exists on the role of TLRs in each of the aforementioned disorders (16, 17), but limited experience is available on pooled information about MetS. This systematic review aims to provide the most recent data about the TLR types expressed in the context of MetS.

Materials and methods

Outcome/ Measures definition: The primary outcome in the current review was the expression (qualitative and quantitative) of TLRs in every cell/tissue and at every level .

Search strategy: We searched international databases until February 2017. We considered PubMed/Medline, ISI web of Science, Scopus, Google Scholar, EMBASE and OVID without limiting for age range, time, and language.

The following terms were used: ‘‘Metabolic Syndrome’’ OR ‘‘Mets’’ AND ‘‘Toll like receptor’’ OR ‘‘Toll like’’ OR ‘‘TLRs’’ OR ‘‘TLR’’. We did not include “expression” in the search terms, and we looked for it at screening stages. We used MeSH term for MetS in PubMed/Medline search, built search strategies and also looked at the reference list of retrieved articles. Search strategy in PubMed was as follows: (("metabolic syndrome"[All Fields] OR "metabolic syndrome x"[All Fields]) OR MetS [All Fields]) AND ((("toll like receptor"[All Fields] OR "toll like"[All Fields]) OR TLRs [All Fields]) OR TLR [All Fields]).

Inclusion and exclusion criteria: We included all experimental (in vivo, in vitro, interventional) and observational studies. We looked at baseline data of trials to find any expression data appropriate for extraction. We considered both human and animal studies. In the case of finding multiple publications from one study, we selected the more comprehensive one or considered them together.

Selection process: At the first step, the retrieved titles were screened to find relevant articles. Next, the abstracts were screened, and finally the full texts of the recovered papers were screened.

Quality assessment: Our study eligibility criteria, design of studies, sample sizes, measurement methods and estimates were considered to qualify the papers. Two independent reviewers (ZF and MM) qualified the articles and the poor- rated ones were excluded.

Data extraction: The data related to authors, publications features, study population, methods, values of selected measures and main conclusions were extracted.

Results

The search algorithm displaying the number of initial search results and included studies is shown in Figure 1. At the first step, 1373 articles were found in the international databases. After the

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duplicate removal and further two steps of screening processes, 963, 410 and 27 articles were remained respectively. As presented in Table 1, after full text screening and qualifying processes, 13 articles were eligible to be included in final review. (6, 18-29) Altogether, these thirteen studies consisted of eight human studies (18-20, 22, 25-28) with a total population of 732 patients (at least 70% females, with total age range of 15 years and above), as well as five animal studies (mice/murine models) (6, 21, 23, 24, 29).

As presented in Table 2, all human studies displayed increased expression of one or more type of TLRs in the monocytes of MetS patients. The most prevalent types of the receptor with increased expression in humans were TLR 2, 4 and 9.

Three studies on animal models of MetS showed a controlling/regulating role for TLRs especially TLR 9 (21) and TLR 5 (24, 29). Another two studies showed over-expression of TLR 2 (6) and increase in a related protein named Janus Kinase 3(JAK3) in signaling cascade of TLRs (23).

Discussion

Based on the results analyzed, our systematic review revealed uniformly increased expression of TLRs in the context of MetS both in humans and animal models. The main TLRs involved were the types 2, 4, 5 and 9 .

Several studies have shown that TLRs are possible links between obesity /visceral fat accumulation and inflammation and their consequent effects on body tissues (30, 31). Konner and colleagues reported that upon development of obesity, numerous molecular conditions might promote activation of stress kinases, causing peripheral insulin as well as central insulin and leptin resistance (10). Jang and colleagues in their study concluded that TLR-2 in vascular endothelium mediates some pro-inflammatory and "unfolding protein response",which results in impairment of vaso-dilatory effect of insulin and ends in endothelial dysfunction (32). Thompson et al. suggested that continued activation of TLR might result in vascular oxidative stress and thereby would aggravate the process of hypertension and heart failure (33). These links would ultimately result in cardio-metabolic disorders (8) which are common consequences of MetS. Our findings propose some molecular mediators in their pathways.

McMillan et al found that in the mice with over-expression of muscular TLR-4, high-fat diet significantly decreases fatty acid oxidation in muscles in accordance with increased body weight and fat, glucose intolerance, and cellular oxidative damage (34). Frisard et al showed that activation of TLR-4 by lipo-polysaccharides would result in increased glucose consumption and reduced fatty acid oxidation in skeletal muscles (35). These findings suggest that TLR-4 plays an important role in the metabolic reactions in skeletal muscle. This might explain MetS related metabolic disturbances in muscles. Some lipo-polysaccharide endotoxins, originating from gut microbiome, are secreted into blood, and by activating TLRs, lead to a chronic metabolic inflammation status called meta-inflammation (36-38). This is a core pathogenic process in the development of MetS. Our study refers to some TLRs involved in this situation. As is evident from the articles systematically reviewed in this study, many aspects of the relation between TLRs and metabolic/endocrine disorders are well documented. Himes et al showed that mice lacking TLR-2 are substantially protected from diet-induced adiposity, insulin resistance, hypercholesterolemia, and hepatic steatosis (6). Cuevas et al speculated that there is a positive feedback between the expression of TLR4, myeloid differentiation primary response gene 88(MYD88) and plasminogen activator inhibitor-1(PAI-1) in the adipose tissue of obese individuals that develop metabolic complications (18).

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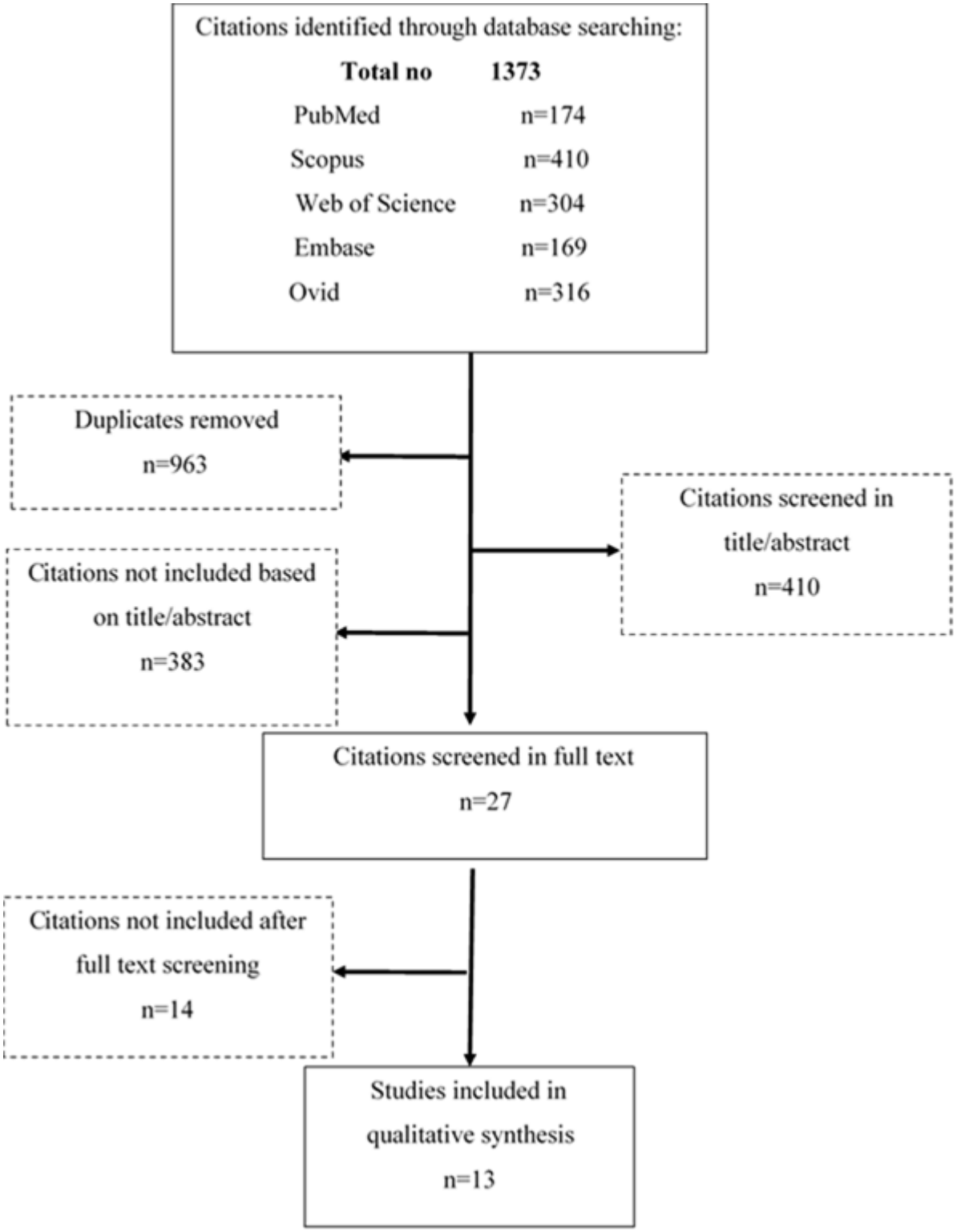


Figure 1. Flowchart of the review.

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Table 1. Characteristics and findings of the Studies included in the qualitative synthesis.

First author, study year	Type of study	Population	Main conclusions
Cuevas AM, 2017 [18]	Prospective study	40 obese men and women, with BMI between 30 and 45kg/m2 at a single hospital (Clinica Las Condes) in the city of Santiago, Chile	A significant correlation between the gene expression of TLR4 in subcutaneous fat with the subcutaneous and visceral expression of MYD88.
Zwolak A, 2016 [19]	Experimental cohort study	48 individuals, all Caucasians of Polish descent, who had never been treated due to liver diseases before control group comprised 22 healthy individuals	A significant association between NAFLD and BMI, MetS and inflammatory parameters, and TLR4. TLR4 expression in peripheral blood mononuclear cells was increased in overweight and NAFLD individuals with metabolic syndrome compared to control groups
Devaraj S, 2015 [20]	Experimental study	Subjects aged 21–70 years with MetS (n= 45) and healthy control subjects (n = 37) from Sacramento County, California	Increased endosomal TLR-9 expression in Mets compared to controls that correlate with increased nuclear NFkB expression in the monocytes of these subjects, with no change in TLR3 protein.
Hong CP, 2015 [21]	Experimental study	Mice	TLR9 signaling involved in regulating adipose tissue inflammation and controlling obesity and Mets.
Jialal I, 2015 [22]	Experimental study	Subject aged 21-69 years, with nascent MetS (n = 28) and control subjects (n = 25) from Sacramento County, California.	There was a significant increase in Adipose Tissue (AT) TLR2 and TLR4 protein in MetS compared to controls.
Mishra J, 2015 [23]	Experimental study	Mice	The essential role of JAK3 in promoting mucosal tolerance through suppressed expression and limiting activation of TLRs thereby preventing intestinal chronic low grade inflammation (CLGI) and associated obesity and Mets.
Chassaing B, 2014 [24]	Experimental study	Mice	Similar to previous studies from TLR-5 null mice. These mice had Mets and more prone to develop colitis compared to their sibling controls.
Jialal I, 2014 [25]	Experimental study	Subjects aged 21-69 years with nascent MetS (n=37) and healthy controls (n=32) from Sacramento County, California.	SCD14 reflects increased monocyte TLR-4 protein and activity in nascent Mets.
Orsatti CL, 2014 26	Cross-sectional experimental study	1 Brazilian women (age≥45 years and amenorrhea≥12 months 31	TLR-2 and TLR-4 expressions were associated with increased pro-inflammatory cytokines, IL-6 and TNF-a, with no association with biomarkers of MetS
Hardy OT, 2013 [27]	Experimental study	17 adolescents (three boys and fourteen girls) between 15 and 19 years from the University of Massachusetts Worcester and Boston campuses	Their study suggest that activation of TLRs may be partially responsible for the increased systemic inflammation seen in adolescents with Mets
Jialal I, 2012 [28]	Experimental study	Subjects aged (21–70 years) with MetS (n=49)and healthy control subjects (n =41) from Sacramento County, California	They make the novel observation that both TLR2 and TLR4 expression and activity are increased in the monocytes of patients with Mets and could contribute to increased risk for diabetes and CVD. This study provides novel data of increased TLR-2 and 4 in Mets serving
Himes RW, 2010 [6]	Experimental study	Mice	The obesity and other chemical features of Mets can be prevented in TLR-2 deleted mice using two physiologically relevant diet models.
Vijay-Kumar M, 2010 [29]	Experimental study	Mice	The malfunction of the innate immune system (in this study TLR-5 deficient mice) may promote the development of Mets.

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Table 2. Summary of the main findings of studies included in the review.

	First author, study year	TLRs activation	Tissue/cells
Human	Jialal I, 2012[28] Jialal I,2015[22] Orsatti CL, 2014[26]	TLR2 and 4 ↑	Monocytes
	Hardy OT, 2013[27]	TLRs ↑	Monocytes
	Zwolak A, 2016[19] Jialal I, 2014[25] Cuevas AM, 2017[18]	TLR4 ↑	Monocytes and adipose tissue
	Devaraj S, 2015[20]	TLR9 ↑ with no changes in TLR3	Endosomal, monocytes
Animal	Hong CP, 2015[21]	TLR9 for regulating role	Adipose tissue
	Himes RW, 2010[6]	TLR2 ↑	Liver and Primary epididymal adipose tissue
	Mishra J, 2015[23]	JAK3 for signaling cascade of TLRs ↑	Frozen colon tissue
	Vijay-Kumar M, 2010[29] Chassaing B, 2014[24]	TLR5 for controlling and regulating role	Proximal colon and adipose tissue

Zwolak et al showed that TLR4 expression in peripheral blood mononuclear cells was increased in overweight individuals with metabolic syndrome compared to control groups (19). Devaraj et al demonstrated increased endosomal TLR-9 expression in Mets compared to controls (20).

Hong et al. found a dramatic increase of macrophages as well as T helper cells in the adipose tissue of TLR-9-deficient mice compared to wild-type mice. They showed that TLR-9 signaling is involved in regulating the inflammation of adipose tissue and controlling obesity and the MetS (21). Jialaland colleagues showed a significant increase in Adipose Tissue TLR2 and TLR4 protein in MetS compared to controls (22). Mishraet al study demonstrates the essential role of JAK3 in promoting mucosal tolerance through suppressed expression and limiting activation of TLRs thereby preventing intestinal chronic low grade inflammation and associated obesity and MetS (23). Chassaingand coworkers showedTLR-5 null mice had Mets and were more prone to develop colitis compared to their sibling controls (24). Jialal et alstudy reflects increased monocyte TLR-4 protein and activity in nascent MetS (25). Orsatti and colleagues showed that TLR-2 and TLR-4 expressions were associated with increased pro-inflammatory cytokines, IL-6 and TNF-α, with no association with biomarkers of MetS. (26) Hardy et al study suggests that activation of TLRs may be partially responsible for the increased systemic inflammation seen in adolescents with MetS (27). Jialal and co-researchers made the novel observation that both TLR2 and TLR4 expression and activity are increased in the monocytes of patients with Mets and could contribute to increased risk for diabetes and CVD (28). And finally Vijay-Kumar et al showed thatThe malfunction of the innate immune system (in their study TLR-5 deficient mice) may promote the development of Mets (29). Our systematic review pools and summarizes their findings.

Several other disorders such as autoimmune thyroid and pancreatic diseases and septic dysregulation of the hypothalamic pituitary adrenal axis have been linked to TLR activation (39) and its gene polymorphism (40-42) as well. These receptors have also shown wide range relations with diabetes (43-46) and non-alcoholic fatty liver disease (47-49, 17).

On the other hand, Zhang and colleagues reported that environmental circumstances may override the genetic aspects of TLRs and their interaction with gut microbime (50). Based on their suggestion, researchers should consider the environment-induced alterations of gut microbiota as a significant confounding factor in this relation.

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From the multisided interaction of TLRs with every component of MetS, it is anticipated that TLRs have crucial role in the aggregation of the MetS components and their coincidence named MetS. To the best of our knowledge, no previous systematic review has summarized the types of TLRs expressed in MetS.

Study limitations and strengths

This systematic review considered published data, and not the grey literature. A variety of tissues of interest and methods for observation existed in the included articles. There were no uniform quantitative data to conduct a meta-analysis. The strength of the study is its novelty as a systematic review in this field.

Conclusion

This systematic review provides thirteen citations which have worked on the expression of TLRs in MetS. From all the data stated, it is apparent that there is constant over-expression of TLR receptors 2, 4, 5 and 9 in the monocytes and some other cells of humans and animals afflicted with MetS. This systematic review confirms the close relation of innate immune system with MetS and proposes the types of TLRs involved. These distinguished TLRs might be used in future studies for developing agents affecting the situation.

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Conflict of interest

None declared.

Author contribution

All authors contributed to the idea, design and conduct the study and drafting the manuscript. All authors approved the final version to be submitted.

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