



A Comprehensive Insight into Potential Roles of Taurine on Metabolic Variables in Type 2 Diabetes: A Systematic Review

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Abstract

Background: Prevention and management of type 2 diabetes mellitus (T2DM), as a major, non-communicable disease with increasing prevalence, is one of the major human challenges. The aim of this systematic review is to summarize current studies about the potential roles of taurine in T2DM, to identify knowledge gaps and to provide recommendations for the way forward.

Methods: The literature search was performed in PubMed, SCOPUS, Embase, ProQuest and Google Scholar electronic databases to December 2019. All studies investigating the impacts of taurine in T2DM which met the inclusion criteria were eligible.

Results: Out of 1381 articles found in the search, 12 were included. Findings of taurine supplementation on glycemic control in T2DM showed improving effect of taurine on fasting and postprandial blood glucose, serum insulin level, insulin resistance, function of beta cells, and insulin sensitivity. But, the results for Hemoglobin A1c and homeostatic model assessment-insulin resistance (HOMA-IR) were contradictory. Also, taurine reduced total cholesterol, TG, and low density lipoprotein-cholesterol (LDL-C) levels, however, the evidence on high density lipoprotein-cholesterol (HDL-C) was insufficient. Findings didn't support antioxidative role of taurine in T2DM.

Conclusion: As a whole, taurine has potential to improve glycemic status and dyslipidemia. However, more clinical trials are needed to explore precise mechanisms underlying taurine on metabolic variables, oxidative stress, and inflammatory biomarkers, according to the recommendations for future directions.

Introduction

Diabetes mellitus is one of the major threats to human health in the 21st century.¹ The prevalence of this disease is rising dramatically. The prevalence of this disease is estimated to be 439 million in 2030s and 642 million in 2040s.² Type 2 diabetes mellitus (T2DM), which accounts for approximately 85% of all diagnosed cases of diabetes, can be as a result of genetic predisposition, environmental risk factors or a combination of these two factors.³ In general, increased levels of inflammation and oxidative stress caused by chronic hyperglycemia play a central role in the pathogenesis of T2DM.⁴ Chronic hyperglycemia can cause macrovascular (such as coronary artery disease, peripheral vascular disease and cerebrovascular disease) and microvascular complications (including retinopathy, nephropathy and neuropathy).⁵ On the other hand, increased oxidative stress and proinflammatory factors are the most important factors to induce insulin resistance.⁶ In general, insulin resistance, inflammation, and oxidative

stress play a critical role in the pathogenesis of T2DM.⁷ Nowadays, naturally occurring antioxidants are the focus of recent interest due to providing a protection against T2DM-induced cellular damage.⁸

Taurine (2-aminoutanosulfonic acid) is a sulfuric amino acid and the most abundant amino acid in the human body.⁹ In mammals, taurine is found almost abundantly in irritable tissues such as the brain, heart, eyes, platelets, secretory tissues, and the skeletal muscle.¹⁰ Taurine is supplied both exogenously from the diet and endogenously from hepatic metabolism of methionine and cysteine.¹¹ Taurine not only has regulatory role on osmotic pressure, cell membrane stabilization, bile salts synthesis, detoxification, and calcium homeostasis, but also acts as antioxidant, and anti-inflammatory agent.^{9,12-14} Serum levels of taurine decreases in oxidative stress-related diseases such as T2DM, metabolic syndrome and obesity.¹⁵ Studies have shown that taurine has anti-obesity,¹⁶

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antihypertensive,¹⁷ hypoglycemic,¹⁸ cholesterol-lowering,¹⁹ anti-cancer,²⁰ neuroprotective,²¹ and anti-atherosclerotic properties.²²

The impact of taurine on type 1 diabetes has been well studied. Accordingly, taurine provides protection against metabolic disorders, oxidative stress, inflammation occurred in type 1 diabetes. However, T1DM may not necessarily reflect the pathologic processes that observed in T2DM. Hence, studies are needed to address specific effect of taurine on T2DM considering the molecular mechanisms. In spite of several studies that examined the effect of taurine supplementation on metabolic variables in T2DM, there is no systematic review report to summarize these effects and explain the directions for future studies.

Methods

Search strategy

This study was designed based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) protocol for reporting systematic reviews and meta-analyses.²³ To find related studies, two researchers independently conducted an extensive systematic search in online databases in PubMed, SCOPUS, Embase, ProQuest, and Google Scholar using [MeSH keywords (“taurine”) and (“diabetes mellitus” or “type 2 diabetes” or “type II diabetes” or “type “noninsulin-dependent diabetes mellitus” or “NIDDM”)] and [(“taurine”) and non-MeSH keywords (“hyperglycemia” or “insulin secretion” or “diabetic” or “T2DM” or “fasting blood sugar” or “glycemic outcomes” or “fasting blood glucose” or “HOMA-IR” or “B-cell function”)]. There are no restrictions on the timing and type of studies in the search strategy. Only articles published in English language until December 2019 were included.

Inclusion and exclusion criteria

The titles and abstracts of studies in the online database were screened by two researchers independently based on inclusion and exclusion criteria. Inclusion criteria for eligible studies including: 1) all clinical trials studies on the effect of taurine supplementation on metabolic indices in patients with T2DM. 2) Observational studies that have evaluated the association between serum levels of taurine and metabolic indicators in patients with T2DM. 3) All animal studies have examined the effect of taurine supplementation on the metabolic variables in animal models of T2DM.^{24,25} In addition, In the current systematic review, we excluded letters, comments, short communication, abstracts, those conducted on pregnant and lactating women, and in vitro studies. In addition, reference lists of relevant studies were reviewed to prevent missing any publication. Additionally, duplicate citations were removed at the end of the search.

Data extraction

In first, after receiving the full text of eligible studies, two investigators independently screened the articles. In the

next step, the following information was extracted from each eligible study using a standardized data collection form and research question:²⁶ first author’s name, year of publication, country of origin, type of study, methods or models, quantity and gender of participants, dosage and duration of the intervention, and main outcomes. Any disagreements between the researchers were resolved through discussion until consensus was reached.

Results

Analysis of the data

Regarding potential roles of taurine on metabolic variables in T2DM, totally, we found 1381 publications by initial search strategy, among which 248 studies were duplicate and removed. Out of residual 1133 articles, 1119 were identified as unrelated after rereading for titles and abstracts. When investigating full texts of articles, additional 2 studies were excluded because of insufficient information (*i.e.* letters, comments, short communication, conferences, congresses, and abstracts). Finally, 12 papers were selected for inclusion in this systematic review.²⁷⁻³⁸ Currently, two clinical trials are also ongoing which their results have not been yet published.^{39,40} A flowchart of the process of studies selection has been summarized in Figure 1.

Characteristics of the included studies

Of the 12 studies selected, 8 were conducted on animal models, 4 were based on human models (Table 1). Majority of the animal studies used spontaneous model of T2DM including Otsuka Long- Evans Tokushima fatty (OLETF) rats,^{28,30,31,33} GK rats,²⁹ and ob/ob rats.³⁴ Two studies induced diabetes by high fat and high sugar diet combined with streptozotocin (STZ)³² and feeding the genetically hyperglycemic KK mice a high calorie diet.²⁷ Of the 8 animal articles identified, 7 articles included measures of blood glucose,^{27-30,32-34} 4 included measures of insulin,^{29-31,34} and 6 evaluated lipid profile.^{28-30,32-34} oxidative stress indices were assessed by the selected animal studies.^{27,30} In 7 of 8 animal studies, animals had received a diet supplemented with 1% to 5% taurine. The duration of the taurine supplementation varied from 7 days to 11 months. Of two studies with case-control design, only one evaluated the association between plasma taurine levels with FBG, insulin in T2DM patients.³⁸ Hemoglobin (Hb) A1c was measured in both case-control studies.^{36,38} Two included trials used 1.5 g and 3 g for 3 months and 4 months, respectively.^{35,37} The primary outcomes measured in trials were related to glycemic response and oxidative stress.

Overview of taurine

Taurine (IUPAC name: 2-aminoethanesulfonic acid, chemical formula: $\text{NH}_2\text{CH}_2\text{CH}_2\text{SO}_3\text{H}$) is a semi-essential β -sulphonated amino acid containing a sulfonic group instead of carboxylic group and an amino group that synthesized predominantly in the liver through cysteine sulfinic acid pathway.⁴¹ Hypotaurine, as an

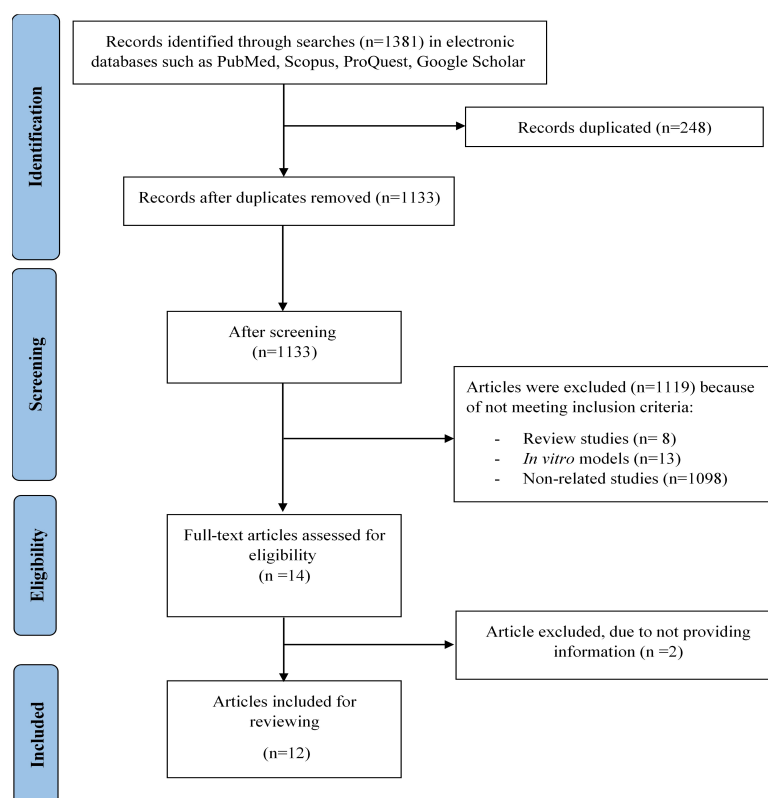


Figure 1. Flow diagram of the literature search and study selection process.

intermediate in the biosynthesis of taurine, is formed following dioxygenation of cysteine to cysteine sulfinic acid by cysteine dioxygenase and the decarboxylation of cysteine sulfinic acid catalyzed by sulfinoalanine decarboxylase.⁴² Ultimately, hypotaurine dehydrogenase allows the oxidation of hypotaurine to taurine.⁴² In spite of endogenous biosynthesis (50-125 mg/day in adults), taurine should be mainly supplied via dietary intake.^{43,44} As a whole in mammals, the balance between de-novo-synthesis of taurine, dietary intake, renal reabsorption, and excretion as taurine-conjugated bile acid and unconjugated taurine in urine determines total taurine pool¹⁰. Seafood such as shellfish, especially scallops, mussels, and clams presents the highest content but red meat as well as dark meat of turkey and chicken is the major dietary sources of taurine.⁴⁵ Taurine is absorbed through mammalian small intestine by mediating Na⁺- and Cl⁻-dependent, transporter TauT and the H⁺-coupled, pH dependent transporter PAT1,¹⁰ the latter appears to play principal role in the high blood levels of taurine following a taurine-rich meal.⁴⁶ In a healthy person, brain, heart, and muscles are the main taurine storage sites. Taurine is also high in the liver, lungs, kidney, salivary glands, bone, and testis.⁴⁷ While taurine distribution modifies under diabetic conditions resulting from selectively impaired transport of taurine.⁴¹

Biological activities of taurine

Taurine has been shown to target a variety of processes, such as neuroprotection, osmoregulation, retina function, immunomodulation, hepatoprotection, bile salt

formation, and atherosclerosis.^{14,48} Accumulating evidence demonstrates that antioxidant and anti-inflammatory properties of taurine are involved in the protective impact of taurine on the various conditions.⁴² Taurine induces antioxidant effects via several mechanisms. First, taurine directly interacts with reactive hypochlorous acid to form taurine chloramine, which is a more stable compound than hypochlorous acid.⁴⁹ Second, decreased levels of taurine reduce complex I activity because of suppressing the biosynthesis of specific mitochondrial proteins, such as NADH-ubiquinone oxidoreductase chain 6 as a subunit of complex I. The reduction in complex I activity decreases oxidation rate of NADH by the respiratory chain leading to overproduction of superoxide. Therefore, taurine is capable of decreasing superoxide formation and subsequent oxidative stress.^{50,51} Third, taurine could normalize the activities of antioxidant enzymes.⁵² Taurine could also suppress inflammatory responses through forming taurine chloramine.⁵³ Taurine chloramine was shown to inhibit activity of nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) and to suppress gene expression of nitric oxide, IL-6, IL-8, TNF- α , and prostaglandin E2.^{54,55} Antioxidative and anti-inflammatory effects of taurine also caused its hypoglycemic impacts.⁵⁶ Other mechanisms by which taurine regulated glycemic response include stimulation of insulin secretion and insulin-sensitizing action. Taurine increases insulin secretion via inhibition of ATP sensitive K⁺ channels.^{57,58} Insulin-sensitizing effect of taurine is also mediated through augmenting insulin receptor substrate (IRS)-1/2, tyrosine and

protein kinase B (Akt) serine phosphorylation levels.^{59,60} Conjugation of taurine with bile acids forms taurocholic acid, taurodeoxycholic acid, tauroolithocholic acid, and taurocheno- deoxycholic acid which are the major bile salt.⁶¹ Bile salts not only play principal role in the intestinal digestion and absorption of lipids, but also remove the cholesterol from the plasma.¹¹ In addition to increasing fecal excretion of cholesterol, taurine increases the gene expression and activity of cholesterol 7 α -hydroxylase, the regulatory enzyme in the conversion of cholesterol to bile acids, leading to increased conversion rate of cholesterol to bile acids, decreased arterial lipid accumulation and atherosclerotic lesions.⁶²⁻⁶⁴

Taurine and glycemic control in T2DM

Seven animal studies evaluated the responses of glycemic biomarkers, insulin levels or insulin resistance to taurine administration. In 3 of 7 studies that examined blood glucose levels in animal models, the supplementation with taurine was shown to decrease glucose levels.^{30,32,33} According to Harada *et al.* (2004) the taurine-supplemented diet (3% in drinking water) reduced postprandial blood glucose, and insulin resistance in rats with T2DM after 9 weeks, whereas no significant within and between groups changes were found following 9 or 21 days of the same dosage of taurine.³⁰ Borck *et al.* (2018) treated leptin-deficient obese mice with 5% taurine for 11 months and reported significant improvement in insulin sensitivity, glucose tolerance and glycaemia.³⁴ In addition, plasma and total islet insulin content as well as insulin release from isolated pancreatic islets were significantly decreased in response to taurine, after treatment with 11.1 and 22.2 mM glucose, but not for 2.8 mM. However, the changes in fasting blood levels of glucose (FBG) and insulin were not significant. This result was consistent with the study by Nakaya *et al.* on T2DM rats that didn't observe significant changes in serum levels of fasting and postprandial blood glucose following consumption of the same dosage of taurine for 9 months.²⁸ In another study, supplementation of diabetic rats feeding a diet supplemented with 1% taurine for 10 weeks significantly increased glucose-stimulated insulin secretion.³¹ However, the authors didn't assess glycemic status. Another animal study on diabetic rats supplemented with 2% taurine for 12 weeks, showed significant decreases in FBG, postprandial glucose, homeostatic model assessment-insulin resistance (HOMA-IR)-IR, and leptin levels without significant changes in HbA1c, HOMA- β , adiponectin levels, and pancreatic beta cell mass.³³ Results from another study by Lin *et al.* (2010) revealed a significant decrease in blood glucose levels following supplementation of diabetic rats with various dosages of taurine (0, 3.4, 2.6, and 2.1mg/kg) for 10 weeks.³²

Two studies with case-control design have so far measured plasma levels of taurine in the patients with T2DM to recognize whether plasma taurine is associated with diabetes mellitus.^{36,38} The results of these studies revealed

significantly lower plasma levels of taurine.^{18,65} In addition, De Luca *et al.* observed lower levels of platelet taurine uptake along with higher levels of platelet taurine release in diabetic patients compared to controls.³⁶ The authors also reported a weakly significant correlation between plasma taurine and HbA1c levels, while, Sak *et al.* didn't find significant association between plasma levels of taurine with FBG, HbA1c and insulin concentrations in the T2DM patients.³⁸ In a clinical trial that evaluated anti-hyperglycemic effects of taurine in T2DM patients, in spite of significant increase in level of whole blood taurine, no changes were seen after consumption of 3000 mg of taurine for 4 months.³⁷ Currently, modulatory effect of taurine on glycemic status is investigating in one ongoing clinical trial with parallel design in which patients with T2DM are receiving either 3000 mg taurine or placebo for 8 weeks. Although, the results of this trial have not been published.⁴⁰

Taurine and dyslipidemia in T2DM

We identified 6 of 8 animal studies examining anti-dyslipideic effects of taurine. In a study conducted by Nakaya *et al.* (2000), the lowering effects of taurine on serum levels of triacylglycerol and cholesterol in the liver were observed in diabetic rats supplemented with 5% taurine for 9 weeks, with no considerable effect on serum levels of high density lipoprotein- cholesterol (HDL-C).²⁸ Borck *et al.* (2018) examined similar dosage of taurine on leptin-deficient obese mice for 11 months and observed significant reduction in plasma TG concentrations.³⁴ Nishimura *et al.* (2002), treated diabetic rats feeding either a cholesterol-free or cholesterol-enriched diet with 3% taurine for 21 or 14d.²⁹ In spite of significant increase in daily excretion of fecal bile acids, the authors reported significant increase in the plasma cholesterol and phospholipids concentrations in diabetic rats fed cholesterol-free diet after 14 days. The changes in triglyceride (TG) concentration, HDL-C level, very low density lipoprotein- cholesterol (VLDL)+low density lipoprotein- cholesterol (LDL-C) levels, and liver cholesterol concentrations were not significant.²⁹ In contrary, 21 days' treatment with taurine led to significant decrease in the plasma levels of cholesterol phospholipid, VLDL+LDL-C, and liver cholesterol concentration along with significant increase in HDL-C levels and daily excretion of fecal bile acids in diabetic rats fed high cholesterol diet, however, the changes in TG level were not significant.³⁶ In another study, the intake of the same dosage of taurine for 9 weeks significantly reduced plasma levels of triacylglycerol.³⁰ The results from Lin *et al.* (2010) in which diabetic rats received various dosages of taurine revealed significant reduction in serum levels of TG, and TC along with significant increase in HDL-C levels after 10 weeks.³² Similarly, according to Kim *et al.* (2012), a diet supplemented with 2% taurine decreased serum levels of TG, TC, HDL-C, and LDL-C in diabetic rats after 12 weeks.³³ Besides, one ongoing clinical trial with parallel design has been registered in Iranian Registry of Clinical Trials in which anti-dyslipidemic effects of taurine are

Table 1. Characteristics of the included studies.

Type of study	Author/date	Source	Model	Results (Taurine group)
Animal	Lim et al./ 1998 ²⁷	South Korea	Rats were divided into 4 groups as follows: normal control, T1DM, genetically hyperglycemic mice without diabetes, T2DM treated with 5% taurine in drinking water for 7 days.	<ul style="list-style-type: none"> –No significant changes in FBG. –No significant changes in hepatic GPX activity of both T1DM and T2DM. –Significant increase in islet GPX activity of T2DM. –No significant changes in glutathione S-transferase activity in T2DM.
	Nakaya et al./ 2000 ²⁸	Japan	Male rats with T2DM were fed a diet supplemented with 5% taurine or a non-supplemented control diet for 9 weeks	<ul style="list-style-type: none"> –Significant decrease in serum levels of TG and TC, total fat, and hepatic levels of TG and TC. –No significant differences in serum levels of HDL-C, fasting and postprandial blood glucose.
	Nishimura et al./ 2002 ²⁹	Japan	Diabetic rats were fed either a cholesterol-free or cholesterol-enriched diet supplemented with or without 3% taurine for 21 (experiment1) or 14d (experiment2).	<p>Experiment 1:</p> <ul style="list-style-type: none"> –Significant increase in TC concentrations. –No significant changes in plasma glucose and insulin levels, TG, HDL-C level, VLDL+LDL-C levels, liver cholesterol concentration in diabetic rats fed cholesterol-free diet. <p>Experiment 2:</p> <ul style="list-style-type: none"> –Significant decrease in the TC, VLDL+LDL-C, and liver cholesterol concentration in diabetic rats fed high cholesterol diet. –Significant increase in HDL-C levels in diabetic rats fed high cholesterol diet. –No significant changes in plasma glucose and insulin levels, and TG concentration in diabetic rats fed high cholesterol diet.
	Harada et al./ 2004 ³⁰	Japan	Male rats with T2DM received a taurine-supplemented diet (3% in drinking water) or normal diet without taurine supplementation for 9 weeks.	<ul style="list-style-type: none"> –No significant changes serum insulin concentration. –Significant increase in lipid oxidation rate. –Significant decrease in postprandial blood glucose, insulin resistance, plasma concentration of TG, fasting and postprandial glucose oxidation rate.
	Kim et al./ 2005 ³¹	South Korea	Diabetic rats were fed a diet supplemented with 1% taurine in drinking water for 10 weeks.	<ul style="list-style-type: none"> –Significant increase in glucose-stimulated insulin secretion. –Significant inhibition of glucose-induced K_{ATP} channel activity in beta cells.
	Lin et al./ 2010 ³²	China	High fat, high sugar diet combined with STZ injection were used to induce T2DM and then diabetic rats were supplemented with various dosages of taurine (0, 3.4, 2.6, and 2.1mg/kg) for 10 weeks.	<ul style="list-style-type: none"> –Significant decrease in blood glucose level, TG, TC. –Significant increase in HDL-C levels.
	Kim et al./ 2012 ³³	South Korea	Diabetic rats were fed a diet supplemented with 2% taurine or a non-supplemented control diet for 12 weeks.	<ul style="list-style-type: none"> –Significant decrease in FBG, postprandial glucose, HOMA-IR, Serum levels of TG, TC, HDL-C, and LDL-C. –No significant differences in body weight, HbA1c, HOMA-β, pancreatic beta cell mass
	Borck et al./ 2018 ³⁴	Brazil	Female leptin-deficient obese mice were orally supplemented or not with 5% taurine for 11 months	<ul style="list-style-type: none"> –Significant improvement in insulin sensitivity, glucose tolerance and glycaemia during the ipGTT test. –Significant decrease in plasma TG concentrations, total AMPK protein, insulin release from isolated pancreatic islets. –No significant changes in body weight, FBG, fasting insulin, plasma TC levels, and hepatic protein content of AMPK, pAMPK/AMPK.

Table 1 Continued.

	Franconi et al./ 1994 ³⁵	Italy	Patients with insulin-dependent diabetes mellitus and non-insulin-dependent diabetes mellitus received 1.5 g/day for 3 months.	<ul style="list-style-type: none"> –Significant increase in taurine levels in both plasma and platelets only in insulin-dependent diabetes mellitus patients. –Significant decrease in arachidonic acid- induced platelet aggregation only in insulin-dependent diabetes mellitus patients. –Significant reduction in the platelet aggregation only in platelet-rich plasma obtained from insulin-dependent patients after addition of taurine in <i>in vitro</i> experiment. –Significantly lower plasma and platelets levels of taurine were observed in insulin-dependent diabetic patients. –Significantly lower platelets levels of taurine were observed in non-insulin-dependent patients.
Human	De Luca et al./ 2001 ³⁶	Italy	Thirty-eight patients with T2DM and 26 healthy control subjects were included in the study to evaluate plasma and platelet taurine content and fluxes.	<ul style="list-style-type: none"> –A weakly significant correlation between plasma taurine and HbA1C levels in the diabetic patients. –Significant decrease in platelet taurine uptake in diabetic patients in comparison to healthy controls. –Significant increase in platelet taurine release in comparison to healthy controls. –Significantly lower plasma and platelets levels of taurine were found in diabetic patients than controls.
	Chauncey et al./ 2003 ³⁷	USA	Thirty-two patients with T2DM received 3000 mg of taurine or placebo for 4 months.	<ul style="list-style-type: none"> –Significant increase in level of whole blood taurine. –No significant changes in glucose, HbA1c, lipids, and insulin levels. –No significant changes in oxidative stress.
	Sak et al./ 2019 ³⁸	Turkey	Fifty-nine patients with T2DM, and 28 healthy control subjects were included in the study to evaluate plasma taurine levels and their relationship with diabetic complications.	<ul style="list-style-type: none"> –No significant correlation between taurine levels with FBG, HbA1c and insulin in the diabetic patients.

AMPK; AMP-activated protein kinase, FBG; fasting blood glucose, GPX; glutathione peroxidase, HbA1c; hemoglobin A1c, HDL-C; high density lipoprotein- cholesterol, HOMA-IR; homeostatic model assessment-insulin resistance, ipGTT; intraperitoneal glucose tolerance test, LDL-C; low density lipoprotein-cholesterol, STZ; streptozotocin, TC; total cholesterol, T1DM; type 1 diabetes mellitus, T2DM; type 2 diabetes mellitus, TG; triglyceride, VLDL; very low density lipoprotein-cholesterol.

investigated in T2DM patients receiving 3000 mg taurine for 8 weeks.⁴⁰

Taurine and oxidative stress in T2DM

Two studies addressed the effect of taurine on oxidative stress in diabetes mellitus.^{27,37} Lim et al. (1998) performed a study focusing on the effect of taurine on the oxidative stress, in diabetic rats.²⁷ Supplementation with 5% taurine for 7 days significantly increased the activity of islet glutathione peroxidase (GPX) in the rats with T2DM, however, the changes in the activities of GPX and GSH S-transferase, hepatic malondialdehyde (MDA) levels and hydrogen peroxide formation were not significant.²⁷ The results from the only clinical trial assessing antioxidative effects of taurine in T2DM that conducted by Chauncey et al. (2003), didn't indicate significant changes in the oxidative stress.³⁷ Currently, antioxidative effects of taurine are exploring through one ongoing clinical trial on T2DM patients

receiving 3000 mg taurine for 8 weeks.⁴⁴ On the other hands, another trial with a focus on the effect of taurine on advanced glycation end products (AGEs) and related receptors has been registered in Iranian Registry of Clinical Trials in which T2DM patients have been assigned to either taurine (3000 mg) or placebo groups for 8 weeks.³⁹

Discussion

The results of this systematic review show that taurine supplementation in animal models of T2DM has potential to improve fasting^{30,32,33} and postprandial blood glucose,^{30,33,34} serum insulin levels,^{33,34} insulin resistance^{30,33}, function of beta cells,^{31,33} and insulin sensitivity.³⁴ However, the results for other glycemic indexes such as HbA1c and HOMA-β were contradictory. Also, clinical trials on the effect of taurine on glycemic status were insufficient. Similarly, taurine supplementation suppressed hyperglycemia in T1DM

animals.^{66,67} However, the results of human studies on the glycemic consequences of taurine in T1DM were inconsistent.⁶⁸⁻⁷⁰

Taurine supplementation in early life delays the onset of diabetes by increasing the normal β -cell viability and pancreatic islet cell numbers, reducing β cells apoptosis, and normalizing morphophysiology and secretory functions of pancreatic cells.⁷¹ Potential mechanisms by which taurine improves the function, viability, and morphology of beta-pancreatic cells in the insulin-resistant animal models include upregulation of the gene expression of Maf-A, PDX-1 and GLUT-2, stimulation of K_{ATP} channel function, along with calcium channel activity and voltage sensitivity.^{58,72,73} The ability of taurine in increasing β -cell viability is mediated through downregulating proinflammatory agents such as NF- κ B, TNF- α , and monocyte chemoattractant protein (MCP)-1.^{15,74} It is well known that taurine induces glucose-mimetic effect in T1DM through preventing progressive declines in the number and the size of pancreatic islets.^{75,76} Also, taurine impedes hyperglycemia-induced stresses in animal models of T1DM, leading to decreased levels of diabetes complications and prolonged survival of animals.⁷⁷ Other protective mechanism of taurine against hyperglycemia in T2DM include normalizing the alterations in the pancreatic islet mitochondria and preventing compensatory growth of β -cell mass as well as insulin hypersecretion during insulin-resistant state.^{78,79}

In liver, taurine suppresses the enzymes involved in gluconeogenesis and increases the gene expression of glycogenesis enzymes and thereby decreases hepatic production of glucose.^{57,78} Also, taurine reduces the function of glucagon in the liver.⁸⁰ Taurine also improves insulin sensitivity with increases in the expression of the UCP1 protein in the mitochondria of adipose tissue, ultimately leading to stimulation of white adipose tissue to brown one.^{81,82} In addition, taurine administration may be able to upregulate gene expression of peroxisome proliferator-activated receptors (PPAR)- α and PPAR γ coactivator (PGC)-1 α in white adipose tissue that involved in insulin sensitizing activity.⁸³ In the muscle, taurine increases insulin sensitivity along with glucose uptake through stimulation of AMP-activated protein kinase (AMPK) pathway activity.³⁴ Activation of AMPK enhances insulin signaling following the phosphorylation of phosphatidylinositol-3-kinase (PI3K) and Akt and incorporation of GLUT-4 into cell membrane.^{84,85}

Dyslipidemia is one of the major complications of T2DM, which can increase the risk of cardiovascular disease in these patients.^{86,87} The results of this systematic review showed that taurine reduced total cholesterol (TC),^{32,33} TG,^{28,30,32-34} and LDL-C levels,^{28,32,33} however the results for HDL-C were insufficient. Anti-dyslipidemic effect of taurine were mediated by several pathways. Taurine stimulates the activity of hepatic cholesterol 7 α -hydroxylase along with the synthesis of 3-hydroxy-3-methylglutaryl-CoA reductase and thereby enhances cholesterol catabolism

into bile acids and hepatic LDL-C depletion.¹⁹ Also, there were significant decrease in hepatic cholesterol ester pool and significant increase in LDL-C receptors following taurine administration.¹⁶ Lowering effect of taurine on TG was mediated by phosphorylation of Akt, suppression of sterol regulatory element-binding protein (SREBP)-1c and downregulation of enzymes involved in fatty acid synthesis.⁸⁸

Oxidative stress plays a vital role in the pathogenesis and complications of T2DM.⁸⁹ Several possible mechanisms have been suggested for the antioxidant activities of taurine. In general, taurine reduces oxidative stress by decreasing ROS production, scavenging ROS, and interfering with ROS activity.¹⁵ The main source of ROS in the cells is mitochondria, which is neutralized by the superoxide dismutase (SOD), catalase (CAT) and GPX enzymes after mitochondrial leakage.^{90,91} Increased levels of ROS results in destruction of pancreatic β cells, impaired insulin production,⁹² insulin resistance,⁹³ and hyperglycemia.⁹⁴ Studies suggest that taurine suppresses the production and scavenging of superoxide in the mitochondria.⁹⁵ Taurine interferes with cellular effects of ROS by increasing the activity of SOD,^{96,97} CAT^{65,98} and GPX^{27,98} enzymes. Regardless of the favorable antioxidant role of taurine in previous studies and its role in improving diabetes, no support has been verified in the T2DM. In contrary, the results from studies on T1DM provided evidence showing antioxidant activities of taurine.^{97,99,100} Collectively, taurine supplementation suppressed ROS production and ROS-mediated apoptotic death of cells in STZ-treated animals by increasing the activity of antioxidant enzymes such as SOD and CAT along with downregulating the expression of cytochrome P450 2E1, as a potential source of ROS.^{97,99} Therefore, further studies in this field appear to be needed in the future for more accurate results.

Knowledge gaps and recommendations for future directions

Adiponectin is an anti-inflammatory adipokine that improves insulin signaling in muscle and liver cells. Studies show that taurine can increase adiponectin levels.^{54,101,102} This adipokine binds to receptor 1 (AdipoR1) in skeletal muscle and receptor 2 (AdipoR2) in the liver and activates the AMPK pathway. The AMPK pathway is the target of many drugs to control diabetes mellitus.¹⁰³ One animal study reported stimulatory effect of taurine on AMPK in T2DM.³⁴ Activation of AMPK has been found to regulate glucose hemostasis and insulin sensitivity by stimulating the β -oxidation of fatty acids.¹⁰⁴ Tyrosine phosphorylation of IRS and following activation of AMPK and AKt in skeletal muscle cells improve mitochondrial function along with insulin signaling pathway and enhance GLUT4 translocation to the cell surface and glucose uptake.^{103,105-112} (Figure 2).

In liver, activation of AMPK pathway upregulates gene expression of PGC-1 α .¹¹³ Elevated levels of PGC-1 α leads to upregulation of PPAR- α and downregulation of Acetyl-

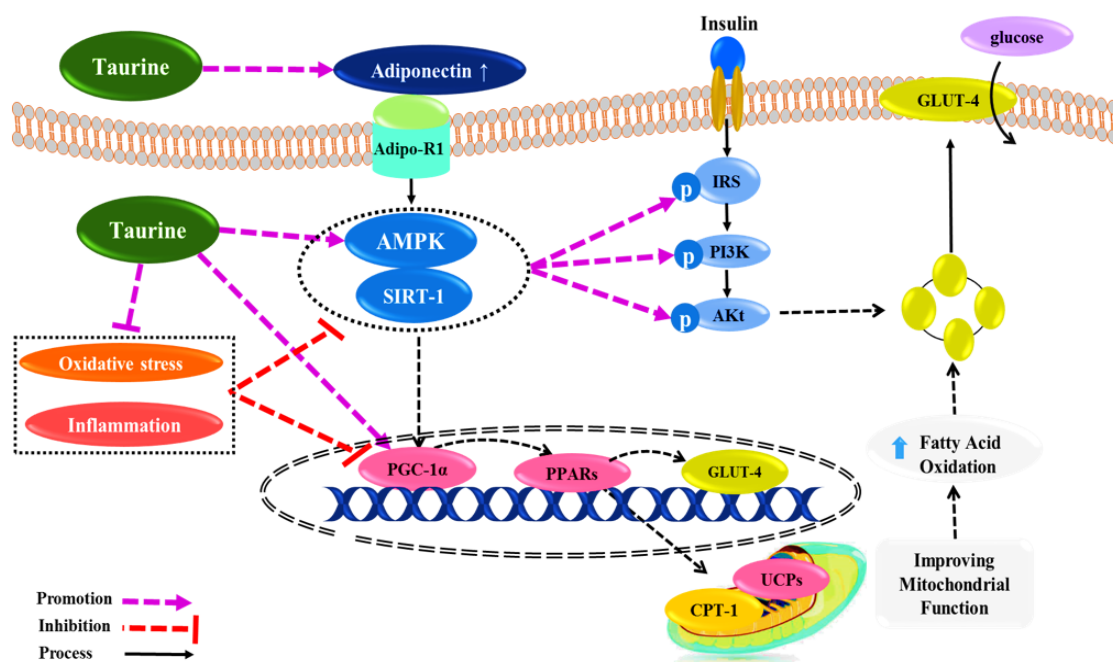


Figure 2. Possible mechanisms of the taurine potential roles on cell signaling pathways in skeletal muscle in type 2 diabetes.

CoA carboxylase (ACC) and SREBP-1c gene.¹¹³ Reduced SREBP-1c, as a transcription factor regulating lipogenesis in the liver, leads to reduced lipogenesis.^{113,114} On the other hand, PGC-1α suppresses the expression of forkhead box protein O1 gene (FOXO-1) and then the GLUT-2, leading to reduced gluconeogenesis and increased glycogenesis.¹¹⁵⁻¹¹⁷ In other words, PGC-1α regulates gluconeogenesis in the liver by binding to FoxO1 to control expression of key enzymes involved in the gluconeogenic pathway¹¹⁸ (Figure 3).

In addition, elevated levels of inflammatory cytokines

upregulate NF-κB, inhibit AMPK and PGC-1α pathway and thereby induce dyslipidemia and hyperglycemia.¹¹⁹ Given to the beneficial effects of taurine on adiponectin levels and AMPK, evaluating the effect of taurine on adiponectin levels and the expression of genes involved in AMPK signaling may be recommended as a new perspective for future studies. Also, the present study showed that no human studies to date have examined the effects of taurine on oxidative stress indices and inflammatory biomarkers, so anti-inflammatory effect of taurine could be considered in future trials.

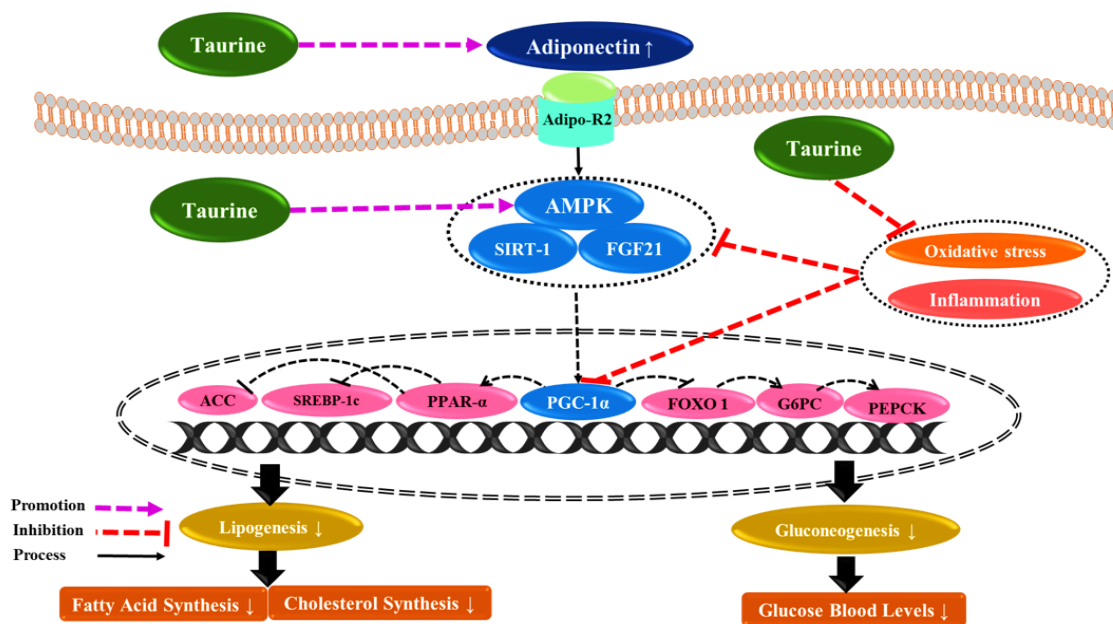


Figure 3. Possible mechanisms of the taurine potential roles on cell signaling pathways in hepatocyte in type 2 diabetes.

Production of AGEs following chronic hyperglycemia is one of the most important agents involved in the pathogenesis of T2DM complications (microvascular and macrovascular). Studies have shown that antioxidant compounds can suppress AGEs production.¹²⁰ In animal models, taurine suppresses the production of AGEs,^{121,122} so it is recommended that future studies investigate the effect of taurine on AGEs in patients with T2DM.

Conclusion

As a whole, the findings of this systematic review showed that taurine can improve glycemic indexes and lipid profile in T2DM, but further clinical trials are needed to confirm these results. In addition, studies around the effects of taurine on oxidative stress biomarkers were inadequate. It would be best to explore the precise mechanisms of the potential role of taurine in T2DM in future studies based on recommendations for future directions.

Ethical Issues

The thesis proposal was approved by Medical Ethics Committee of Tabriz University of Medical Sciences (IR.TBZMED.REC.1397.682).

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Conflict of interest

The authors declare they have no conflict of interest.

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