Association of Adiponectin Level and Type 2 Diabetes Mellitus (T2DM): A Systematic Review and Meta-analysis

Daniel Setiawan Nathan, Hoo Yumilia
Division of Endocrinology and Metabolism
Departement of Internal Medicine
Faculty of Medicine Maranatha Christian University / Immanuel Hospital
Correspondence : dokterdanielsetiawan@gmail.com

Abstract

Introduction: Experimental and epidemiologic evidence has accumulated that supports a beneficial role of adiponectin, a major cytokine secreted from adipocyte, in glucose metabolism. Mechanistic studies show that adiponectin improves insulin sensitivity and inflammation, important mechanisms in the development of type 2 diabetes.

Method: This study is a systematic review and meta-analysis conducted to see the relationship between adiponectin levels and the incidence of type 2 diabetes mellitus. The research involved in this review was taken from journal databases, such as: Pubmed, Google Scholar, and Sage Pub. The included studies were studies involving both diabetic and non-diabetic humans, the study clearly showed blood sugar levels and adiponectin levels of the study sample.

Result: Researchers included 7 reviewed studies for analysis discussing adiponectin as a risk factor for type 2 DM and related complications.

Conclusion: There is an inverse relationship between adiponectin levels and the incidence of diabetes and associated vascular complications.

Keyword: Adiponectin**;** Diabetes; Risk Factor; Vascular Disease

Introduction

Diabetes mellitus is a group of metabolic disorders characterized by prolonged hyperglycemia, resulting from impaired pancreatic insulin

secretion and / or impaired insulin action in the periphery.[1] Diabetes is a chronic disease and requires ongoing treatment to prevent acute and long-term complications. The role of genetic factors in the incidence of type 2 DM has been proven from various reports. Subjects with one or both parents suffering from type 2 diabetes had a 2-6 times higher risk of developing diabetes than subjects without a parental history of diabetes.[2]

Prevalence of type 2 DM has increased very sharply in the last two decades, where from the number of sufferers of 171 million people in 2000 worldwide, it is expected to increase to 366 million people by 2030. Due to the high mortality and morbidity rates associated with type 2 diabetes, the increasing prevalence of this disease, has become a serious health problem and is a major economic burden in the health care system.[3,4]

Type 2 diabetes mellitus is a low-grade chronic inflammatory condition. On the other hand, low-grade chronic inflammatory conditions are predictors of the incidence of type 2 diabetes later in life. Pro-inflammatory and anti-inflammatory cytokines play a role in the regulation of blood glucose and the body's energy balance.[5] Adiponectin, a protein secreted by adipocytes and functions as an anti-inflammatory, can improve insulin sensitivity in the periphery so as to prevent the occurrence of RI.[6,7]

Adiponectin, a hormone almost exclusively secreted by adipocytes, participates in several anti-inflammatory and insulin-sensitizing processes. Experimental and epidemiologic evidence has accumulated that supports a beneficial role of adiponectin, a major cytokine secreted from adipocyte, in glucose metabolism. Mechanistic studies show that adiponectin improves insulin sensitivity and inflammation, important mechanisms in the development of type 2 diabetes.[8]

In humans, several prospective studies have consistently shown a lower risk of type 2 diabetes among those with higher baseline levels of circulating adiponectin.[9] Krakoff et al reported that hypoadiponectinemia can predict the occurrence of type 2 diabetes in normal people. The same

phenomenon was also found in subjects with RI and metabolic syndrome (MetS).[10]

That study has also proven that there is an association between decreased levels of adiponectin and the occurrence of RI and the risk of developing type 2 diabetes in adults. However, this is actually too late because the pathogenesis of type 2 DM has occurred many years before the onset of the disease.[10] This review aims to examine the effect of adiponectin on the risk of developing type 2 diabetes and related complications.

Methods

This study is a systematic review and meta-analysis conducted to see the relationship between adiponectin levels and the incidence of type 2 diabetes mellitus. The research involved in this review was taken from journal databases, such as: Pubmed, Google Scholar, and Sage Pub. The included studies were studies involving both diabetic and non-diabetic humans, the study clearly showed blood sugar levels and adiponectin levels of the study sample.

The search keywords used were “adiponectin level” and “type 2 diabetes mellitus (T2DM)” ("adiponectin"[MeSH Terms] OR "adiponectin"[All Fields] OR "adiponectin s"[All Fields] OR "adiponectine"[All Fields] OR "adiponectins"[All Fields]) AND ("level"[All Fields] OR "levels"[All Fields]) AND ("diabetes mellitus, type 2"[MeSH Terms] OR "type 2 diabetes mellitus"[All Fields]) AND "T2DM"[All Fields]) AND ((y_10[Filter]) AND (ffrft[Filter]) AND (clinicaltrial[Filter] OR randomizedcontrolledtrial[Filter])). Researchers removed research published before 2011 and then searched for full-text articles. Researchers only included original articles.

This study uses the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) model, where the researchers first typed keywords in each database, then found 125 articles on Pubmed, 1,754 articles on Google scholar, and 725 articles on Sage. pubs. The

researcher then changed the time span of the last 10 studies, until finally 25 articles were found on Pubmed, 976 articles on Google Scholar, and 97 articles on Sage Pub. Researchers screened titles (type 2 diabetes, human studies, etc.) until there were 7 articles on Pubmed, 23 articles on Google Scholar, and 6 articles on Sage Pub. Until finally the researchers assessed the feasibility of the study and included only 7 studies **(Fig 1)**.

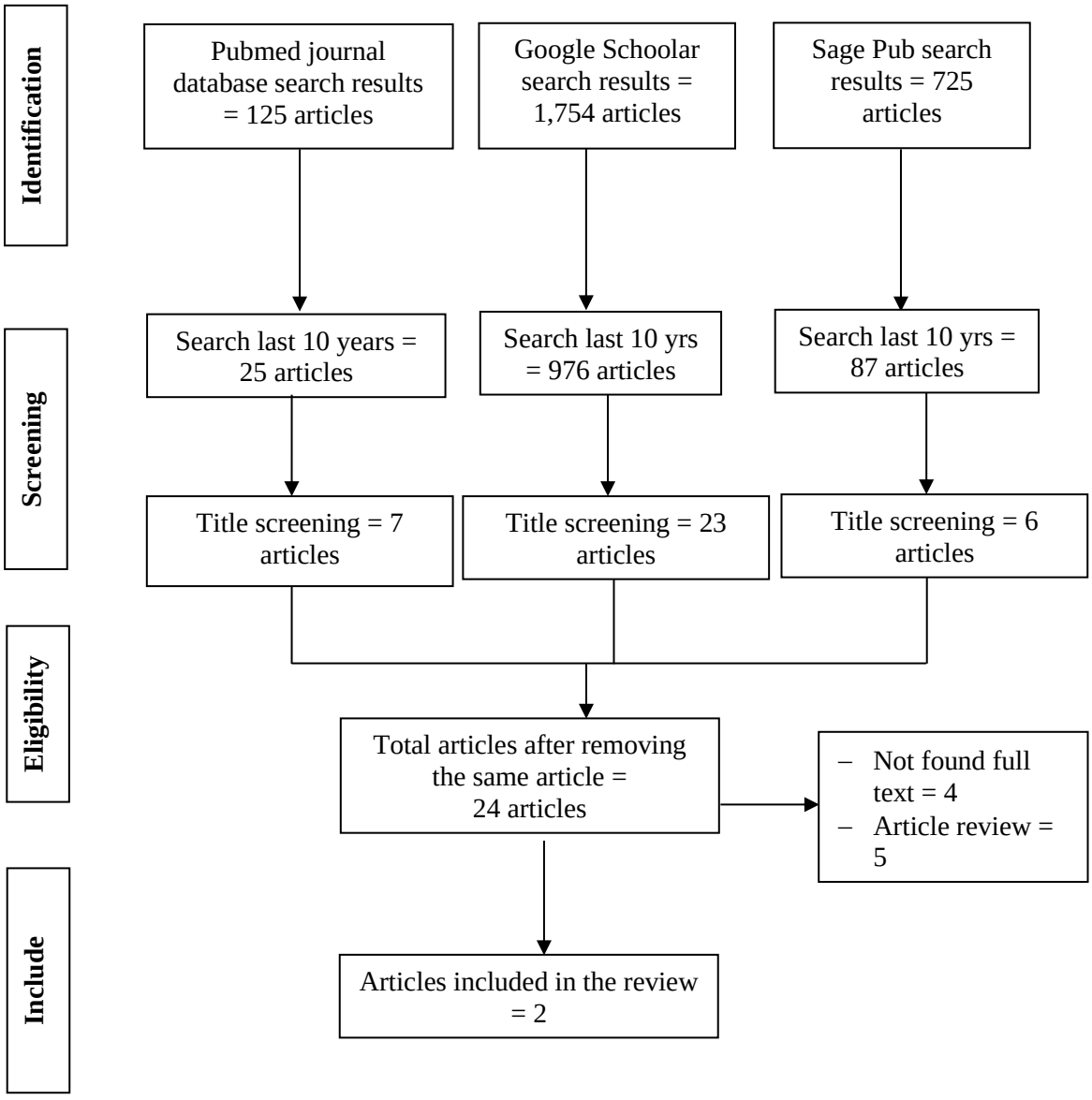

Figure 1. Article search flowchart

Result

Researchers included 7 reviewed studies for analysis. Wang (2018)[11] conducted a study that aimed to determine the risk of type 2 diabetes based on adinopectin levels. Yamamoto et al (2014) conducted research involving 4591 Japanese employees who attended a comprehensive health screening in 2008 and received health screening in 2011. During 3 years of follow-up, 217 diabetic cases were newly identified. Of these, 87% had a prediabetes at baseline. Serum adiponectin level was significantly, inversely associated with incidence of diabetes, with odds ratios (95% CI) adjusted for age, sex, family history, smoking, alcohol drinking, physical activity and BMI for the lowest through highest quartile of adiponectin.[12]

Lindberg (2014) also conducted a prospective study including 666 patients with ST-segment elevation MI, without diabetes, treated with percutaneous coronary intervention, from September 2006 to December 2008 at a tertiary cardiac center.[13] Ullah (2020) recruited 65 diabetes patients and 50 healthy control subjects. Serum levels of fasting blood glucose (FBG), total lipid profile levels, adiponectin, and insulin were measured in all subjects.[14]

There are several studies linking adinopectin levels to blood vessel complications in DM patients. The first study was conducted to investigate the serum levels of adiponectin (APN) and adiponectin receptor 1 (AdipoR1) in patients with type 2 diabetes mellitus (T2DM) combined with macrovascular complications (MVC), as well as their correlation with clinical parameters.[15]

Table 1. The Literature Include in This Study

Author	Origin	Method	Sample Size and Population	Period	Result	Outcame
Wang (2018)[11]	Singapore	Case control	63,257 adult population	2011	The median (interquartile) concentration of adiponectin was 6.7 (5.2–8.3) µg/mL in men and 8.1 (6.4–10.5) µg/mL in women, and it was 6.7 (5.2–8.3) µg/mL in the cases and 8.4 (6.5–10.8) µg/mL in the controls.	The adiponectin-T2D association remained unchanged after adjusting for inflammation and dyslipidemia markers, but substantially attenuated with adjustment for insulin sensitivity and/or glycaemia markers. Overall evidence indicates that higher adiponectin levels are associated with decreased T2D risk in Chinese and other populations.
Su (2019)[15]	China	Randomized Controlled Trial (RCT)	60 sample (T2DM patients were divided into 2 groups according to the presence of MVC)	No Describe	The mean level of adiponectin in DM patients was 7 µg/mL and 5 µg/mL in complicated DM patients.	Serum levels of APN and AdipoR1 are significantly lower in T2DM group and T2DM + MVC group, showing lowest value in T2DM + MVC group. APN and AdipoR1 levels may influence glucose and lipid metabolism in T2DM patients.

Author	Origin	Method	Sample Size and Population	Period	Result	Outcame
Jiang (2018)[16]	China	Case control	60 sample (T2DM with PAD)	January 2015 and December 2016	The mean level of adiponectin in DM patients with mild PAD is 11 µg/mL, moderate PAD 10,72 µg/mL, and 6,31 µg/mL in severe PAD.	C1q tumour necrosis factor–related protein 9 and adiponectin were higher in diabetes mellitus with severe PAD than DM with mild and moderate PAD groups. Logistic regression analysis showed C1q tumour necrosis factor–related protein 9 was independently associated with the severity of peripheral arterial disease (odds ratio = 0.272, 95% confidence interval = 0.08–0.927, p = 0.037).
Yamamoto (2014)[12]	Japan	Prospective study	4591 Japanese employees (Normal population who attended a comprehensive health screening in 2008)	2011	Adiponectin levels in those without diabetes and with diabetes were 7.93 (4.09) µg/mL and 6.82 (3.57) µg/mL, respectively.	Results suggest that higher levels of circulating adiponectin are associated with a lower risk of type 2 diabetes, independently of overall and intra-abdominal fat deposition, and that adiponectin may confer a benefit in both persons with and without insulin resistance.

Author	Origin	Method	Sample Size and Population	Period	Result	Outcame
Lindberg (2014)[13]	Denmark	Prospective study	666 patients with ST-segment elevation MI, without diabetes, treated with percutaneous coronary intervention	September 2006 to December 2008	Low adiponectin levels remained an independent predictor of T2DM (hazard ratio [HR] 5.8 [2.3–15.0]; P < 0.001)	Low plasma adiponectin was associated independently with increased risk of developing T2DM in a linear dose-response relationship. Even in patients with low glucose, adiponectin still added significantly to the prognostic value, as the risk of developing T2DM was higher in patients with low adiponectin/low glucose compared with patients with high adiponectin/low glucose. However, the risk increased by ∼10-fold in patients who were characterized by the combination of low adiponectin and high blood glucose.

Author	Origin	Method	Sample Size and Population	Period	Result	Outcame
Ullah (2020)[14]	KSA	Prospective study	65 diabetes patients and 50 healthy control subjects	No Describe	The adiponectin serum levels had a mean of 4.837 ± 0.321 and 7.336 ± 1.081 in T2DM cases and controls, respectively	Anthropometric and biochemical profiles are significantly associated with the risk of T2DM. Serum adiponectin levels were reduced in diabetics as opposed to controls. In females, rather than males, reduced adiponectin was associated. It is suggested that variable concentrations of adiponectin can lead to an increased risk of obesity, T2DM, insulin resistance, and metabolic syndrome. Further, the development of adipocytokines as biomarkers may be helpful in managing the risks of metabolic syndrome complications.

Author	Origin	Method	Sample Size and Population	Period	Result	Outcame
Sharma (2020)[17]	India	Cross Sectional Case Control study	120 diabetic patients	No Describe	Adiponectin in patients with diabetes was lower (6.55±0.66) than prediabetes (9.72±0.31) and controls (10.81±2.24)	MDA level were established to be augmented in poor controlled T2DM and is positively correlated with progression of diabetes while adiponectin is negatively correlated with diabetes progression furthermore adiponectin high level is associated with low risk of cardio-metabolic complication and low risk of macro vascular complication in patient with T2DM.

The second study conducted by Jiang et al (2018)[16] involved 200 patients with type 2 diabetes mellitus had ankle–brachial index examined in this cross-sectional study, 60 patients with ankle–brachial index of 0.9 were diagnosed with peripheral arterial disease and further classified into mild, moderate and severe group with Vivid 7 diagnostic apparatus.

Discussion

Adiponectin is a hormone and protein secreted by adipose tissue and has a role in physiological processes in the body, including regulation of the satiety center, energy balance, homeostasis, angiogenesis and blood pressure regulation. Evidence has shown that one or more of the following: These adipokines can interfere with insulin signaling and cause RI in the early stages of pre-diabetes.[2]

Adiponectin inhibits the synthesis and action of TNF-, whereas TNF-α has a negative effect on adiponectin transcription process. Leptin increases the synthesis of IL-6 and TNF- by macrophages and also activates macrophages. Insulin resistance increases the synthesis of TNF- and IL-6, on the other hand, the expression of resistin will be increased by these cytokines.[18,19]

These adipokines play a role in maintaining glucose hemostasis throughout the body, either by modulating gluconeogenesis in the liver or regulating energy demands and hunger in the brain. The purpose of releasing these hormones is to maintain the body's metabolic and energy balance. Several adipokines secreted by adipose tissue such as resistin, leptin and adiponectin apparently affect insulin action in the periphery and oxidation of fat cells so that they are directly related and cause RI.[18,19]

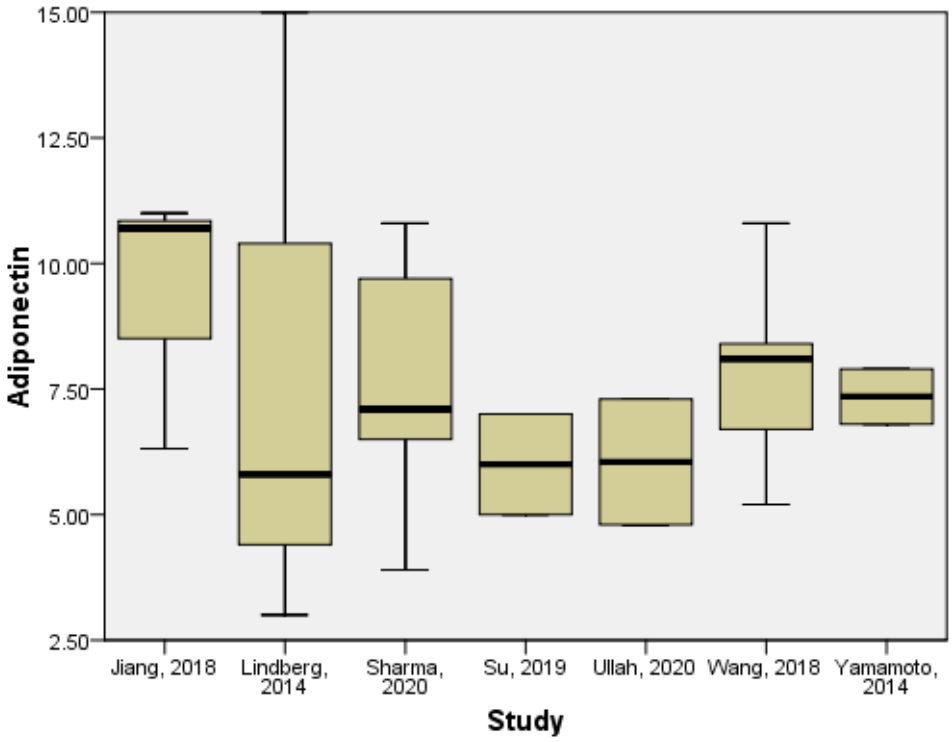

Figure 2. Boxplot shows mean adiponectin levels

The study demonstrated a strong dose-dependent relationship between higher plasma adiponectin levels and a lower risk of T2D, which did not appear to be dependent on pre-existing T2D risk factors, including lipids, inflammatory biomarkers (hs-CRP), randomized glucose. and insulin. In addition, the inverse relationship was significantly stronger among overweight/obese subjects than their lean counterparts. Furthermore, adiponectin significantly increased the reclassification of T2D risk in this population.[11]

Yamamoto showed serum adiponectin level was significantly, inversely associated with incidence of diabetes, with odds ratios (95% confidence interval) adjusted for age, sex, family history, smoking, alcohol drinking, physical activity and body mass index (BMI) for the lowest through the highest quartile of adiponectin of 1 (reference), 0.79 (0.55–1.12), 0.60 (0.41–0.88) and 0.40 (0.25–0.64), respectively (P-value for trend <0.01).

This association was materially unchanged with adjustment for VFA instead of BMI.[12]

After further adjustment for both homeostasis model assessment of insulin resistance and hemoglobin A1c, however, the association became statistically nonsignificant (P-value for trend=0.18). Risk reduction associated with higher adiponectin levels was observed in both participants with and without obesity or insulin resistance at baseline.[12]

Ullah (2020) juga menunjukkan levels of serum adiponectin were lower in the T2DM cases than in the healthy controls. The results of our study are comparable to those of previous studies in which reduced adiponectin levels were demonstrated to be independent of age, gender and BMI in T2DM patients. The major factor contributing to this difference is the underlying insulin resistance in type 2 diabetic patients. Insulin is the hormone that mediates the secretion of proteins, including adiponectin, from the adipose tissue and this adiponectin provokes the sensitivity of insulin.[14]

Studies have shown that adiponectin improves insulin sensitivity by stimulating glucose utilization and fatty acid oxidation in the skeletal muscle and liver through improving AMP-activated protein kinase.[8] Animal studies have shown that adiponectin levels drop in parallel with reduced insulin sensitivity, before the increment in glycemic levels.[20] Moreover, the stratified analysis from the current meta-analysis suggested that lower adiponectin levels may contribute to an increased T2D risk through pathways independent of other important T2D pathogenic mechanisms such as dyslipidemia and inflammation.[12,21]

Although adiponectin is an adipose-specific protein and its concentration reduces with increasing level of obesity, the current cohort study together with previous studies have shown that adjustment for markers of obesity, such as BMI or CT-assessed abdominal fat area, did not materially change the association between adiponectin and T2D risk, suggesting that low adiponectin levels could be associated with higher T2D

risk through pathways that may not be related to systemic or regional fat deposition.[12,21]

Su et al (2019) found that serum APN and AdipoR1 levels were negatively correlated with SBP and DBP. Expressions of APN and AdipoR1 were also obviously correlated with FBG, TC, LDL-C HDL-C. And APN defect might promote diabetic progression and increase the risk of hypertension and cardiovascular disease.[15] Hussain et al. suggested that genetic alterations in the coding gene for APN could significantly influence disease development and serum lipid concentrations in T2DM patients.[22]

The low adiponectin level may enhance the formation of small dense LDL particles, which are most detrimental in vessels and typical in insulin resistance. It is possible that adiponectin may have a direct role on HDL catabolism. It has been reported that adiponectin deficiency may impair the HDL synthesis in the liver.[22] Jiang et al. reported that serum APN was negatively correlated with peripheral arterial disease onset in T2DM patients.[16]

Adipocytokine is being extensively studied world-wide since the past decade because of its remarkable insulin sensitizing property (IR is the major problem in T2DM) as well as antiatherogenic action (dyslipidemia, commonly associated with T2DM, is responsible for atherosclerotic complications of T2DM), thereby playing an important role in delaying and suppressing the metabolic derangements, which result in IR, T2DM, metabolic syndrome and complications of diabetes including vascular and cardiac.[23]

These two important functions of adiponectin involves myriads of interrelated molecular mechanisms, which interconnect it with other diabetogenic/antidiabetic adipokines as well as with many physiological and biochemical processes associated with maintenance of energy balance from metabolism of carbohydrates and lipids. Because of such widespread metabolic involvement, an attempt has been made to discuss the pathophysiological role of this key adipocytokine in detail, which in concert

with its siblings appears to play an important role in linking T2DM with obesity.[23]

Conclusion

There is an inverse relationship between adiponectin levels and the incidence of diabetes and associated vascular complications.

References

1. International Diabetes Federation. Diabetes. Brussels: IDF; 2017.
2. Fauci AS, Jameson JL, Kasper D, et al. Harrison's Principles of Internal Medicine 19th Edition. New York: McGraw-Hill Education; 2018.
3. Soelistijo SA, Lindarto D, Decroli E, et al. Pedoman Pengelolaan dan Pencegahan Diabetes Melitus Tipe 2 Dewasa di Indonesia. Jakarta: PB Perkeni; 2019.
4. American Diabetes Association. Diagnosis and Classification of Diabetes Mellitus. Diabetes Care. 2016;62–9.
5. Yan W, Q QY, Mody N, et al. The adipokine lipocalin 2 is regulated by obesity and promote insulin resistance. Diabetes. 2007;56:2533–40.
6. Kriketos AD, Greenfield JR, Peake PW, et al. Inflammation, Insulin Resistance, and Adiposity. Diab Care. 2004;27:2033–40.
7. Ouchi N, Kihara S, Funahashi T, et al. Reciprocal association of C-reaktive protein with adiponectin in blood stream and adipose tissue. Circulation. 2003;107:671–4.
8. Kadowaki T, Yamauchi T, Kubota N, et al. Adiponectin and adiponectin receptors in insulin resistance, diabetes, and the metabolic syndrome. J Clin Invest. 2006;116(7):1784–92.
9. Li S, Shin HJ, Ding EL, et al. Adiponectin levels and risk of type 2 diabetes: a systematic review and meta-analysis. JAMA. 2009;302(2):179–88.

10. Krakoff J, Funagashi T, Stehouwer CD, et al. Inflamatory markers, adiponectin,and risk of type 2 diabetes in the Pima Indian. Diab Care. 2003;26:1745–51.
11. Wang Y, Meng RW, Kunutsor SK, et al. Plasma adiponectin levels and type 2 diabetes risk: a nested case-control study in a Chinese population and an updated meta-analysis. Sci Rep. 2018;8:406–9.
12. Yamamoto S, Matsushita Y, Nakagawa T, et al. Circulating adiponectin levels and risk of type 2 diabetes in the Japanese. Nutr Diabetes. 2014;4:130.
13. Lindberg S, jensen JS, Pedersen SH, et al. Low Adiponectin Levels and Increased Risk of Type 2 Diabetes in Patients With Myocardial Infarction. Diabetes Care. 2014;37(11):3003–8.
14. Ullah MI, Atif M, Alameen A, et al. Determination of Serum Adiponectin Levels in Type 2 Diabetes Patients of the Saudi Population in the Al-Jouf Region. Rom J Diabetes Nutr Metab Dis. 2020;27(3):257–62.
15. Su N, Zhao N, Wang G, et al. The Effects of Adiponectin and Adiponectin Receptor 1 Levels on Macrovascular Complications Among Patients with Type 2 Diabetes Mellitus. Cell Physiol Biochem. 2019;52(2):225–31.
16. Jiang W, Tang Q, Zhang L, et al. Association of serum C1q tumour necrosis factor-related protein 9 with the severity of lower extremity peripheral arterial disease in type 2 diabetes patients. Diab Vasc Dis Res. 2018;15:270–3.
17. Sharma R, Satyanarayana P, Anand P, et al. Adiponectin Level Association with MDA in the Patients with Type 2 Diabetes Mellitus. Biomed Pharmacol J. 2020;13(2):78–89.
18. Gregor FM, Hotamisligil SG. Adipocyte stress: The endoplasmic reticulum and metabolic disease. J Lipid Res. 2007;48:1905–14.
19. Lefterova IM, Mullican ES, Tomaru T, et al. Endoplasmic reticulum stress regulates adipocyte resistin expression. Diabetes.

2009;58:1879–86.

20. Hotta K; Matsuo K; Ueoka H; et al. Meta-analysis of randomized clinical trials comparing Cisplatin to Carboplatin in patients with advanced non-small-cell lung cancer. J Clin Oncol. 2004;22:3852–9.
21. Hanley AJ, Wagenknect LE, Norris JM, et al. Adiponectin and the incidence of type 2 diabetes in Hispanics and African Americans: the IRAS Family Study. Diabetes Care. 2011;34(10):2231–6.
22. Hussain MK, Deli FA, Algenabi AHA, et al. Adiponectin gene polymorphisms as a predictor for development of type 2 diabetes mellitus in Iraqi population. Gene. 2018;662:118–22.
23. Chakraborti CK. Role of adiponectin and some other factors linking type 2 diabetes mellitus and obesity. World J Diabetes. 2015;6(15):10–7.