Review

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Jamie Rausch *, Kaitlyn E. Horne, Luis Marquez

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Review

The Effects of Adipose Tissue Dysregulation on Type 2 Diabetes Mellitus

Jamie Rausch [1,*], Kaitlyn E. Horne [2] and Luis Marquez [2]

[1] Indiana University

[2] Independent Research

* Correspondence: rauschj@iu.edu; Tel.: +1-260-257-6811

Abstract: In this review, we provide evidence that adipose tissue dysregulation (ATD) plays an important role in Type 2 Diabetes Mellitus (T2DM) development, progression, and prognosis. As such, adipokines (hormones released from adipose tissue) are valuable in monitoring, diagnoses, and treatment of disease states. Specific adipokines, leptin and adiponectin, have already shown to be valuable in this aspect, and their ratio (the leptin-to adiponectin ratio or LAR) may be more valuable than either adipokine individually.

Keywords: adipose tissue dysregulation; type 2 diabetes mellitus; leptin; adiponectin; leptin-to-adiponectin ratio

1. Introduction

For nearly four decades, there has been an understanding that excess adipose tissue is positively, directly correlated with a diagnosis of Type 2 Diabetes Mellitus (T2DM).[1–4] Despite knowing this, the exact mechanism through which adipose tissue dysregulation (ATD) stimulates diabetes disease formation and progression, has not been fully elucidated. With the discovery of adipose tissue functioning as an endocrine organ,[5–8] further details of the pathway have been identified. The purpose of this paper is to review current literature related to T2DM prevalence, influence of T2DM on public health, ATD and how it effects T2DM, and why this connection is important to consider in future research and clinical practice.

2. Overview of T2DM

2.1. Disease Description and Pathophysiology of T2DM

Discussing T2DM pathophysiology is a critical component in understanding and mitigating ATD. In line with the latter, it is important to note that type 1 diabetes mellitus (T1DM) accounts for only about 5 to 10% of newly diagnosed cases of diabetes mellitus.[9] Whereas, T2DM can be attributed to 90 to 95% of newly diagnosed cases of diabetes.[9] A chronic metabolic disorder, resulting from multiple pathophysiological pathways, T2DM is indicated by defects in insulin secretion and uptake, regularly elevated levels of blood glucose levels, or both.[10–14] Diagnosis occurs when an individual has one or more of the following indicators: glycated hemoglobin (HbA1c) ≥ 6.5%, fasting blood glucose ≥ 126 mg/dL or 2-hour post-prandial glucose ≥ 200 mg/dL.[14] T2DM often occurs as a comorbid condition in individuals with other chronic diseases such as obesity, cardiovascular disease, and depression.[15–17] Recently, T2DM has seen an unexpected rise in both adolescents and children, in part due to increased rates of global obesity in all age groups.[18–21]

T2DM is highly influenced by the blending of genetic, lifestyle, and environmental risk factors that contribute to inflammation and ATD. Genetics, passed from generation to generation, predispose inheriting individuals to obesity, insulin resistance, and even inflammation.[22] Lifestyle choices, such as a Western diet, little to no physical activity, and excessive stress can intensify these complications.[23] Inflammation is further aggravated by environmental factors (e.g., pollution) and contribute to T2DM

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development.[24,25] The convergence of these factors directly lead to insulin resistance, inflammation, and T2DM.

2.2. Prevalence and Influence on Public Health

Data extracted from the Global Burden of Disease database indicates that the global burden of T2DM, from 1990-2019, was steadily increasing.[26] Internationally, the prevalence rate of T2DM in 2021 was 10.5%. It is expected to grow to 11.3% by 2030 and, subsequently, 12.2% by 2040.[27] Thus, without significant public health interventions, these rates are likely to continue to increase significantly for the foreseeable future.

When age adjusted, incidence rates for T2DM have been positively correlated with the Sociodemographic Index (SDI),[26] "a summary measure that identifies where countries or other geographic areas sit on the spectrum of development."[28] Much of this correlation can be attributed to how rapid and significant increase has occurred globally over the last several decades. To keep up with high levels of demand and extend shelf life, many food products have become highly processed.[29] Thus, excessive amounts of fats and sugars used in production, are being consumed daily by most populations.[29] This rapid urbanization has also adjusted peoples' lifestyles through changes to their physical environment that result in increased air pollution and decreased physical activity.[30,31]

Each of these lifestyle factors place significant stress on regional healthcare systems, especially those in low SDI regions. Though this is a problem on a global scale, it is disproportionately exaggerated in low SDI communities with decreased access to all forms of healthcare. These communities exhibit decreased compliance to provided management regimens (sometimes related to the ability to purchase needed supplies or medications), directly correlating to an increased burden of disease.[26]

Surprisingly, low SDI regions had a lower incidence of T2DM compared to high SDI regions.[26] When taken at face value, this may be surprising, however it should be considered that high SDI regions have more access to detection methods, leading to earlier diagnoses, management, and subsequently, better outcomes.[26] It should be noted that there is conflicting data regarding a relationship between SDI and prevalence, while some exhibit no relationship others indicate a positive relationship between growing socioeconomic development and prevalence.[26,32]

3. Role of Adipose Tissue in Metabolic Regulation

3.1. Functions of Adipose Tissue

3.1.1. Normal Adipose Tissue Function

The initial perception of adipose tissue function was that it served as an inert storage of energy in the form of triacylglycerol, or triglycerides, the primary form of dietary lipids from fats and oils.[33] Simply put, adipose tissue stored excess fat, released stored fat when dietary intake decreased to meet physical demands, assisted in temperature regulation, and protected internal organs.[33]

The secretory role of adipose tissue is a newer realization. In the 1980's the role of adipose tissue as an endocrine organ was identified.[33–35] Adipose tissue secretes adipokines, hormones released from adipose tissue that go on to influence other bodily actions, such as metabolism and inflammation.[36] Two of these hormones, leptin and adiponectin, have been identified as important regulators of inflammation.[37] In normal weight individuals, leptin and adiponectin are released in regulated levels that maintain homeostasis.[38] Despite this knowledge, normal levels of leptin and adiponectin, exist within very limited parameters (see Table 1). The leptin-to-adiponectin ratio (LAR) is so novel that normal levels have yet to be determined.

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Table 1. Normal values for leptin, adiponectin and their ratio (leptin-to-adiponectin or LAR).

Sex / BMI	Leptin *(ng/ml)*	Adiponectin *(mcg/ml)*	Leptin-to-Adiponectin Ratio (LAR) *(Leptin [ng/ml] / Adiponectin [mcg/ml])*
Male			
= 22	0.5 – 12.5	*Unknown*	*Unknown*
< 25	*Unknown*	5 – 37	*Unknown*
25 - 30	*Unknown*	5 – 28	*Unknown*
> 30	*Unknown*	2 – 20	*Unknown*
Female			
= 22	0.5 – 15.2	*Unknown*	*Unknown*
< 25	*Unknown*	5 – 37	*Unknown*
25 - 30	*Unknown*	4 – 20	*Unknown*
> 30	*Unknown*	4 – 22	*Unknown*

[1] The normal values listed in the table above were available from the Cleveland Clinic.[39,40] All other values for leptin, adiponectin, or the LAR are currently unknown.

3.1.2. Dysregulation Mechanisms

ATD happens very easily, often without any indication of change. As an individual gains excess weight as seen in obesity, cells of adipose tissue (adipocytes) become larger (hypertrophy) and more numerous (hyperplasia).[37] These enlarged adipocytes produce irregular amounts of leptin and adiponectin. Leptin, which has mostly pro-inflammatory actions, is produced in greater amounts than normal.[41] In contrast, adiponectin levels, which has mostly anti-inflammatory actions, is produced in lesser amounts than normal.[42] The changes in the levels of leptin and adiponectin lead to systemic inflammation that contributes to disease development and progression in T2DM.

4. Inflammatory Responses and Insulin Signaling Pathways

The process of systemic inflammation as it relates to adiposity and insulin resistance begins with hypertrophy and hyperplasia of adipocytes, specifically within visceral fat. Increased visceral fat, which envelopes vital organs, releases pro-inflammatory adipokines like tumor necrosis factor (TNF)-α and interleukin (IL)-6 which, in turn, lower levels of adiponectin by downregulation.[43–45]As adipocytes expand and proliferate, the surrounding blood vessels cannot match pace with their growth thus leading to adipocyte hypoxia.[46] Monocytes circulating in the bloodstream sense the dead or dying adipocytes via chemokines.[46] Macrophages from the bloodstream join adipose tissue macrophages (ATMs), or resident macrophages, to surround and phagocytize necrotic adipocytes in a crownlike structure.[44] It is known that in healthy adipose tissue the proportion of ATMs is only about 5-10% whereas in obese individuals this number may be as high as 50%.[47,48] It has been shown that TNF-α and IL-6 compared against adiponectin exhibit a negative correlation contributing to T2DM formation.[49] The continued cycle of hypertrophy and hyperplasia perpetuates the state of low-grade chronic inflammation via inflammatory cytokines.

Chronic inflammation in adipose tissue, caused by ATD, plays a significant role in insulin resistance development, which is a hallmark of metabolic disorders including T2DM. The mechanisms linking adipose tissue inflammation to insulin resistance consist of infiltration of immune cells, pro-inflammatory cytokine release, and signaling pathway disturbance.[50] Adipose tissue expands past its corporal capacity during obesity, leading to cellular stress, oxidative stress, and hypoxia.[51] The resulting pro-inflammatory environment is portrayed by a shift in macrophage polarization (from anti-inflammatory M2 phenotype to pro-inflammatory M1 phenotype) reinforcing the chronic inflammatory state.[52] Furthermore, the infiltration and activation of T cells and B cells are increased, amplifying cytokine production and disrupting insulin signaling.[52]

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5. Clinical Implications of ATD in T2DM

Dysregulated adipose tissue exacerbates T2DM symptoms and complications in a variety of ways. First, as the pro-inflammatory cytokines (e.g., TNF-a and IL-6) are secreted by ATD, they interfere with signaling of insulin receptors which results in insulin resistance.[53] As previously stated, ATD sustains a pro-inflammatory environment with changes to macrophage polarization and increased T and B cell activity, further perpetuating insulin resistance.[52] Glucose metabolism and insulin sensitivity are disrupted by decreased adiponectin production and increased leptin production.[54] Lipotoxicity (the accumulation of transitional lipid materials in non-adipose tissues) throughout liver, muscles, and pancreas results in altered insulin signaling and pancreatic β-cell function.[55] Insulin resistance in muscle and fat tissue diminishes glucose uptake at a cellular level, leading to persistent hyperglycemia.[56] Further, pancreatic β-cells damaged from excessive inflammatory mediators and lipotoxic stress from ATD reduce the production of insulin over time.[57]

Additionally, ATD results in the promotion of comorbidities which add to the inflammation exhibited throughout the body. ATD contributes to vascular endothelial damage through inflammatory mediators, exacerbating cardiovascular disease risk.[58] Increased risk of heart attack and stroke result from ATD's increased dyslipidemia and inflammation which accelerates arterial plaque buildup.[59] ATD also adds to the development and progression of hypertension, dyslipidemia, and non-alcoholic fatty liver disease.[60]

6. Leptin in T2DM

6.1. Physiology – Normal Function

Leptin, produced and secreted primarily by adipocytes, contributes significantly to the regulation of energy balance, hunger, and metabolism by signaling the hypothalamus in the brain to suppress appetite and increase energy expenditure.[61] Typically in lean individuals, leptin enhances insulin sensitivity (in tissues such as liver and muscle) and promotes glucose uptake and fatty acid oxidation, reducing insulin resistance.[53,61,62] Energy homeostasis and metabolism result from symbiotic effects of leptin and insulin.[63,64] Leptin directly induces pancreatic β-cells and constrains insulin secretion in certain conditions and may protect against oxidative stress and lipotoxicity in β-cells.[61,62]

6.2. Pathophysiology – Dysregulation

Leptin resistance often presents in obesity and T2DM. Circulating leptin levels occur higher than normal, however, leptin sensitivity by its receptors is reduced in leptin resistance.[61] The brain then fails to respond to the appetite-suppressing effects of leptin and the result is hyperphagia (overeating), weight gain, and exacerbated insulin resistance.[61,65] As such, leptin resistance leads to a perverse cycle that intensifies metabolic dysfunction. Further heightening hyperglycemia, dysregulation of the pancreatic β-cell signaling pathway by leptin may impair insulin production in T2DM.[65] In obesity and T2DM, leptin also acts as a pro-inflammatory cytokine, causing an inflammatory ripple effect throughout the body.[43,61,62,65]

6.3. Therapeutic Implications

Despite normal leptin affects in appetite and metabolism, leptin resistance creates a barrier to using leptin alone as a therapeutic agent in T2DM.

7. Adiponectin in T2DM

7.1. Physiology – Normal Function

Adiponectin, an adipokine (hormone) secreted mostly by subcutaneous adipose tissue, provides vital functions in the regulation of glucose and lipid metabolism and insulin sensitivity in normal circumstances.[43,62,66] Insulin sensitivity is enhanced by adiponectin in several ways. First, adiponectin

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improves skeletal muscle uptake of circulating glucose.[43,62] Next, adiponectin activates the AMPK (AMP-activated protein kinase) pathway to increase fatty acid oxidation.[43,62] Finally, adiponectin acts directly to suppress glucose production by the liver.[43] Further, adiponectin engages in known anti-inflammatory and anti-atherogenic actions. For instance, adiponectin reduces production of proinflammatory cytokines, such as tumor necrosis factor (TNF)-α,[62] and stimulates production of anti-inflammatory cytokines, such as interleukin (IL)-10.[43,62] Moreover, oxidative stress and endothelial dysfunction are reduced by adiponectin.[43,62]

7.2. Pathophysiology – Dysregulation

In obesity, insulin resistance, and T2DM, adiponectin levels are significantly decreased, resulting in reduced insulin sensitivity, glucose uptake, and fatty acid metabolism.[43,62] Reductions to adiponectin levels further result in increased glucose output from the liver worsening hyperglycemia.[62,67] Low levels of adiponectin relate to chronic low-grade inflammation, endothelial dysfunction, and increased risk of cardiovascular diseases.[67] Although adiponectin, like leptin is produced by adipocytes, adiponectin is inversely correlated with the amount of body fat.[67] Additionally, target tissues may exhibit reduced responsiveness to normal adiponectin levels in adiponectin resistance.[67] In some cases, adiponectin has shown some proinflammatory actions in what is referred to as the adiponectin paradox.[62,66–68]

7.3. Therapeutic Implications

Due to its mostly anti-inflammatory effects, adiponectin offers an opportunity to improve health and disease risk, especially in T2DM, by targeting it with therapeutic interventions. Several lifestyle modifications offer natural increases to adiponectin levels. Increasing dietary intake of omega-3 fatty acids elevate adiponectin levels,[69] as do exercise and weight loss.[67] Pharmaceuticals have also shown promise in improving circulating adiponectin levels. For example, thiazolidinediones (TZDs), sodium-glucose cotransporter-2s (SGLT2)s, gastric inhibitory polypeptides (GIPs), glucagon-like peptide-1s (GLP-1s), angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), statins, and fibrates increase adiponectin levels.[67] Furthermore, new investigational therapies, like adiponectin receptor agonists (AdipoRons), gene therapy, and peptide analogs target adiponectin pathways for therapeutic benefits.[67,70] Adiponectin monitoring may help predict risk, track therapeutic response and even disease progression.[62,67,71]

8. Leptin in T2DM

8.1. Physiology – Normal Function

The leptin-to-adiponectin ratio or LAR is a composite biomarker that represents the balance between leptin (pro-inflammatory, insulin-resistance-promoting) and adiponectin (anti-inflammatory, insulin sensitizing).[67,69,72] In healthy individuals, normally low leptin levels and high adiponectin levels result in a low LAR and is reflective of metabolic homeostasis, normal insulin sensitivity, and low inflammation.[72,73] As such, the LAR provides an integrated view of total adipose tissue function compared to use of leptin or adiponectin alone.

8.2. Pathophysiology – Dysregulation

As previously discussed, with obesity and T2DM, leptin levels increase, and adiponectin levels decrease leading to higher LARs. Higher LARs indicate ATD and increased insulin resistance, worsened glycemic control, endothelial dysfunction, heightened pro-inflammatory state, and risk of cardiovascular diseases.[72,73]

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8.3. Therapeutic Implications

Due to its more accurate indication of ATD, the LAR presents a strong opportunity for a clinical biomarker in predicting risk for insulin resistance and T2DM. Additionally, the LAR could provide feedback in treatment monitoring for lifestyle and pharmacological interventions. In using the LAR as a biomarker, goals should include reducing leptin levels and increasing adiponectin levels. Interventions that have shown improvement in the LAR include: weight loss, exercise, dietary modifications, bariatric surgery, and medications.[68,74,75] Furthermore, the LAR could be used to identify those individuals at high risk prior to disease onset. When interventions are implemented to improve the LAR, it is possible to prevent tissue and organ damage before it occurs.

9. Conclusions

In sum, ATD plays a significant role in T2DM. Specifically, hormones released in abnormal amounts during ATD (leptin and adiponectin) lead to compounding effects throughout the body. Targeting leptin and adiponectin with lifestyle and pharmacological interventions may improve disease symptoms and prognoses while also offering a potential preventative marker in those at risk of T2DM. (Table 2 provides a summary of leptin, adiponectin and the LAR in the context of T2DM.)

Table 2. Summary table of leptin, adiponectin, and the leptin-to-adiponectin ratio (LAR) as they pertain to Type 2 Diabetes Mellitus (T2DM).

Aspect	Leptin	Adiponectin	LAR
Source	Primarily Adipose Tissue	Primarily Adipose Tissue	Derived ratio (leptin/adiponectin)
Normal Role	Regulates appetite and energy expenditure, enhances insulin sensitivity	Enhances insulin sensitivity, anti-inflammatory, promotes lipid oxidation	Reflects balance between pro- and anti- diabetic / inflammatory adipokines
Levels in T2DM	***Increased*** – due to adiposity and leptin resistance	***Deceased*** – due to increased adiposity	***Increased***
Effect on Insulin	***Decreases*** – when resistance develops	***Increases***	High LAR correlates with ***greater insulin resistance***
Inflammatory Role	***Pro-Inflammatory***	***Anti-Inflammatory***	High LAR = ***Pro-Inflammatory State***
Clinical Relevance	Marker of adiposity, leptin resistance, and inflammation	Marker of insulin sensitivity, metabolic health, and inflammation	***Better predictor*** of T2DM risk than either alone
Therapeutic Targeting	Indirect: weight loss, others possible but not clear currently	Targeted by changes to diet, exercise, and pharmacological interventions	Lowered through lifestyle changes, insulin-sensitizing therapy, and modifications of leptin and/or adiponectin
Predictive Value	Moderate alone	Moderate alone	***High predictive value*** for T2DM

Note: LAR = leptin-to-adiponectin ratio; T2DM = type 2 diabetes mellitus.

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