Salivary resistin level and its association with insulin resistance in obese individuals

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Author contributions: Abdalla MMI collected the data and wrote the paper.

Conflict-of-interest statement: The author declares no conflict of interest for this article.

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Manuscript source: Invited manuscript

Specialty type: Endocrinology and metabolism

Country/Territory of origin: Malaysia

Peer-review report's scientific quality classification

Abstract

The escalating global burden of type 2 diabetes mellitus necessitates the implementation of strategies that are both more reliable and faster in order to improve the early identification of insulin resistance (IR) in high-risk groups, including overweight and obese individuals. The use of salivary biomarkers offers a promising alternative to serum collection because it is safer, more comfortable, and less painful to obtain saliva samples. As obesity is the foremost contributory factor in IR development, the adipocytokines such as leptin, adiponectin, resistin, and visfatin secreted from the adipose tissue have been studied as potential reliable biomarkers for IR. Measurement of salivary adipokines as predictors for IR has attracted widespread attention because of the strong correlation between their blood and salivary concentrations. One of the adipokines that is closely related to IR is resistin. However, there are conflicting findings on resistin’s potential role as an etiological link between obesity and IR and the reliability of measuring salivary resistin as a biomarker for IR. Hence this study reviewed the available evidence on the potential use of salivary resistin as a biomarker for IR in order to attempt to gain a better understanding of the role of resistin in the development of IR in obese individuals.

Key Words: Homeostatic model assessment of insulin resistance; Insulin resistance; Obesity; Salivary resistin; Diabetes; Adipocytokines

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Core Tip: The worldwide increased prevalence of obesity-induced insulin resistance (IR) highlights the limitations of the long-term, invasive methods currently being used in detecting and monitoring IR. Measurement of salivary concentrations of adipokines...
such as resistin offers a good alternative to serum collection for early detection and monitoring of glycaemic control among obese individuals. However, there are conflicting findings on the association between resistin and IR. Hence this review of the available evidence aims to provide a better understanding of the role of resistin in the development of IR and the potential use of salivary resistin as a biomarker for IR.

INTRODUCTION

The World Health Organization reported a marked increase in the number of diabetic patients from 108 million in 1980 to 422 million in 2014[1]. There was also a 5% increase in premature mortality from diabetes between 2000 and 2016, and the World Health Organization estimated that diabetes was the seventh leading cause of death in 2016[1]. More recently, in 2020, an epidemiological study estimated that 462 million individuals or 6.28% of the global population are affected by type 2 diabetes mellitus (T2DM), a condition that seems to be more prevalent in developed countries despite the promotion and implementation of a range of public health measures[2].

T2DM is a non-insulin-dependent type of diabetes that was previously largely considered to be a disease of middle and old age. However, during recent decades, there has been a global rise in the prevalence of T2DM among children and young adults[3,4]. This rise has coincided with an increased prevalence of obesity, the foremost contributory factor to insulin resistance (IR) and T2DM[5,6]. The earlier the onset of the disease, the longer its duration and the higher the incidence of complications, which subsequently leads to higher mortality among the younger generation[7].

T2DM is characterized by increased insulin secretion, IR, and impaired glucose tolerance[8]. Early detection of impaired glycaemic control among prediabetics as well as maintenance of good control of the blood glucose level is, therefore, crucial in reducing mortality and delaying the onset of complications[9]. The glucose tolerance test and measurement of glycated haemoglobin are the methods most commonly used for early detection of IR in high-risk individuals[10]. However, the global burdens of T2DM and obesity highlight the limitations of the long-term, invasive screening methods currently employed in the early identification of individuals at high-risk of these two conditions.

PATHOGENESIS OF IR IN OBESITY

The chronic inflammatory state in obesity is known to be a significant pathogenic mechanism for obesity-associated complications[11]. Several polypeptides known as adipokines or pro-inflammatory cytokines that are secreted from adipocytes and adipose tissue macrophages have been found to play a role in inflammatory response as well as in the regulation of energy balance, food intake, and insulin sensitization[12]. Among the known adipokines, adiponectin, leptin, resistin, interleukin-6, tumour necrosis factor-alpha, plasminogen activator inhibitor-1, and monocyte chemoattractant protein-1 have been found to be directly related to the pathogenesis of IR in obesity[13].

Moreover, the chronic inflammatory state in obesity is found to induce a state of oxidative stress that is caused by enhanced production of reactive oxygen species, which is induced by pro-inflammatory cytokines such as tumour necrosis factor-alpha and resistin. It has therefore been suggested that a combination of inflammation and oxidative stress is involved in the process of the pathogenesis of IR[14], as illustrated in Figure 1.

The chronic inflammation, macrophage infiltration, increased leptin level, decreased adiponectin, mitochondrial dysfunction, endoplasmic reticulum stress, and adipocyte apoptosis could be attributed to the adipose tissue hypoxia response and adipocyte...
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Figure 1 Simplified mechanism of obesity-induced insulin resistance.

dysfunction[15], which are found to be associated with the downregulation of insulin receptors resulting in systemic IR[16]. In addition, the inflammation and oxidative stress associated with obesity may be attributed to the aging of the adipose tissue. This process includes molecular changes in the cells, such as deactivation of P53 tumour suppressor and inflammation[17,18]. Oxidative stress is also associated with endoplasmic reticulum stress, which occurs due to excess nutrient intake in obesity[19].

Even with little macrophage infiltrates, lipotoxicity caused due to excess and ectopic fat accumulation in adipocytes, liver, and muscle is found to damage the pancreatic beta cells, leading to T2DM[20]. In addition, lipid overload leads to cellular dysfunction, endoplasmic reticulum stress, activation of pro-inflammatory stress pathways, and occurrence of IR, which may be attributed to the increased production of biologically active lipid intermediates such as ceramides and diacylglycerol[21-23].

IR

Insulin, a pleiotropic peptide secreted by beta cells in the pancreatic islets, regulates the blood glucose level by increasing glucose uptake and utilization in muscles and adipose tissues through stimulating the translocation of glucose transporter 4 to the plasma membrane, inhibiting glucose production in the liver through inhibiting the expression of key gluconeogenic enzymes and promoting lipolysis[24]. The effects of insulin are mediated by the binding of insulin-to-insulin receptors and insulin-like growth factor-1 receptors, which results in phosphorylation of the receptor substrate, followed by activation of the intracellular signalling pathways phosphoinositide 3-kinase/protein kinase B pathway and the mitogen-activated protein kinase pathways[25].

IR is a disease condition in which insulin-dependent cells, such as those found in skeletal muscle, the liver, and adipocytes, are unable to respond properly to the normal circulatory levels of insulin[14]. This inability to respond results in hyperglycaemia, which is caused by decreased removal of glucose from the blood and by increased production of glucose in the liver, the latter of which is associated with decreased fatty acid release from adipose tissues[26].

Studies have proved the usefulness of assessing the serum levels of many of the adipokines, including resistin and adiponectin, as biomarkers for IR[9,27]. The positive correlation between serum and salivary proteome levels[28,29] has attracted attention because of the implication that salivary biomarkers could be used in preference to serum due to the potential benefits of the former in reducing the suffering, pain, and stress associated with serum sampling[30]. The use of salivary biomarkers in diabetes is further supported by the fact that the increased permeability of the basement membrane in diabetes is associated with increased leakage of proteins from serum into
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RESISTIN STRUCTURE AND DISTRIBUTION

Resistin is a cysteine-rich polypeptide that was discovered by Steppan et al.[32]. It has been proposed that resistin is a potential link between obesity and T2DM because it is upregulated in rodent models of obesity and IR and downregulated by insulin sensitizers. Resistin is also known as an adipose-tissue-specific secretory factor, which in humans is encoded by the RETN gene located on chromosome 19[33].

The normal serum level of human resistin ranges from 7 to 22 ng/mL[34]. There are two circulating forms of resistin: high molecular weight resistin, which is the predominant form, and low molecular weight resistin, which is the bioactive form in which bioactivity is initiated by disulphide cleavage in its hexameric structure[35].

Human resistin is quite different from rodent resistin in terms of both its structure and distribution. Murine resistin is a 114 amino acid polypeptide that is produced primarily in white adipose tissue[36], whereas human resistin is a 108 amino acid polypeptide expressed by adipose tissue, particularly visceral fat, pre-adipocytes, adipocytes[37,38], peripheral blood mononuclear cells[39], skeletal muscle[40], the pancreas[41], hypothalamus, adrenal gland, spleen, bone marrow, gastrointestinal tract, lungs[42], pituitary gland[43], and placenta[44]. Here it is worth mentioning that several studies have proved the role of peripheral blood mononuclear cells – the primary producers of human resistin[39,45] – in the inflammatory process involved in the pathogenesis of obesity-induced IR[46,47]. The dissimilar genetic organization of murine and human resistin[48] may be the reason for the conflicting findings on the potential role of resistin as an aetiological link between obesity and diabetes reported in studies on murine vs human resistin.

RESISTIN AS A LINK BETWEEN OBESITY AND IR

Since the discovery of resistin two decades ago, many research studies have been conducted on humans and rodents in order to investigate its potential role as a link between obesity and IR. Higher circulating levels of resistin have been reported in murine and rodent models of obesity compared to lean[32,49], and higher circulating levels of resistin have also been reported in obese individuals compared with lean[50,51] and positively correlated with body mass index (BMI) and visceral fat[51,52]. The increase in resistin in obese rodents may represent a negative feedback mechanism that acts to control adipocyte differentiation[49]. It has been suggested that an increase in the accumulation of adipose tissue, which reflects an increase in adipocyte differentiation and the pool of adipocytes, results in an increase in the secretion of resistin from the adipocytes, where the secreted resistin acts as a paracrine polypeptide that autoregulates its secretion by inhibiting adipocyte differentiation[53]. It has also been reported that resistin increases in parallel with increases in insulin and glucose and decreases in parallel with their decrease, hence the serum level of resistin seems to be regulated by the levels of insulin and glucose[53]. Other regulators of resistin include age, gender, thyroid hormones, and gonadal hormones[54].

Human studies have revealed contradictory findings on the correlation between circulating resistin and IR in T2DM and obesity. Some studies have reported a positive correlation[55-60], whereas others have found a negative[61] or lack of correlation[62,63].

A recent systematic review and meta-analysis conducted in 2019 on the correlation between serum resistin and IR in T2DM and obesity concluded that, overall, the results were in favour of there being a positive correlation between circulating resistin and IR in T2DM and obese individuals with hyperresistinaemia but not in those with normal circulating levels of resistin[64], which implies that resistin needs to reach a certain critical level to cause IR[60]. The meta-analysis was performed on 15 studies that were undertaken during the period 2005–2017 and involved a total of 1227 patients of diverse age, gender, and ethnicity. In the meta-analysis, these patients were classified into 20 clinical groups: 10 with simple T2DM, 7 with simple obesity, 2 with T2DM and obesity, and 1 group of T2DM patients with or without obesity[64]. The difference in resistin concentration among these different groups, which led to conflicting results on the association between resistin and IR, may be explained by the several single nucleotide polymorphisms of the resistin RETN gene in the different ethnic groups studied[65], differences in the levels of insulin and leptin, which have
been found to stimulate resistin expression, and differences in the methods used to assess resistin levels, specifically, commercially available enzyme-linked immuno-sorbent assays have the potential to cross-react with circulating resistin-like molecules, and not all studies assessed for this cross-reactivity before measuring the resistin levels.

**EFFECTS OF INCREASED RESISTIN ON GLUCOSE HOMEOSTASIS**

Overexpression of resistin in transgenic mice has been found to result in the impairment of insulin-dependent glucose transport and uptake by muscles and adipose tissue, which seems to be caused by a reduction in the intrinsic activity of cell-membrane glucose transporters that does not affect insulin receptor signalling. The insulin-independent effect of resistin on glucose homeostasis is supported by a previous study that has shown that resistin induces the expression of a suppressor of cytokine-signalling-3, which functions to inhibit insulin signalling. Resistin stimulates gluconeogenesis in the liver, an action that is evidenced by low hepatic glucose production in resistin gene knockout mice, an effect that is reversed by resistin infusion that causes an increase in the glucose level of approximately 25%. In addition, hyperresistinaemia increased level of fasting glucose, hepatic glucose production, and induced activity of gluconeogenic enzymes.

High levels of resistin stimulate the expression of tumour necrosis factor-alpha and interleukin-6 in both human and murine macrophages via the NF-kB-dependent pathway, which results in IR. In addition, an increased resistin level leads to leptin resistance, which contributes to the development of IR, as illustrated in Figure 2.

**SALIVARY RESISTIN AND IR IN OBESE INDIVIDUALS**

Due to the increased global and economic burden of T2DM, IR, and obesity across age groups, including children and young adults, the need for effective, easy, and non-invasive methods for early detection and monitoring of IR has increased. The use of saliva as a diagnostic tool is evolving not only due to the rapid advances that are being made in the fields of nanotechnology and molecular diagnostics, but also because saliva contains biomarkers that are ideal for early detection and monitoring of oral as well as systemic diseases.

To review the available evidence on the association between salivary resistin and IR in obese individuals, the scientific literature published up to 31 December 2020 was searched in the following databases: PubMed, ProQuest, Scopus, Ovid, Science Direct, Springer Link, and Trip. The search was limited to papers published in the English language. A search of the references in the identified papers was also done to identify any additional relevant papers. At the end of the search process, a total of six papers were identified for review. These papers, which were published between 2011 and 2020, are discussed in ascending chronological order.

The first selected study, conducted by Mamali et al. in Patras, Greece and published in 2011, involved the measurement of resistin in saliva and an assessment of the association between its salivary and serum levels. Salivary and serum resistin was measured using a commercial enzyme immunoassay method. Samples were measured in duplicate. Serum samples were diluted five-fold while saliva samples were diluted three-fold. The study reported a strong positive correlation between the serum and salivary levels of resistin ($r = 0.441, P = 0.003$) with no significant correlation between their levels with age, body fat percentage, or BMI. The ratio of the serum level of resistin to its salivary level was 0.2. The positive correlation between the salivary and serum levels of resistin that was reported indicates that resistin was transported from the blood to saliva, which supports the potential use of the salivary levels of resistin rather than its serum levels for early detection of IR. The absence of a correlation between the salivary as well as the serum levels of resistin with age, BMI, and body fat percentage could be attributed to the characteristics of the participants, who were healthy with almost normal BMI and body fat. It could also be attributed to the measurement method that was used.

A positive correlation between saliva and serum levels of resistin was further evidenced in a 2012 study conducted in China by Yin et al. who investigated for the first time the differences in the serum and salivary levels of resistin in a sample of 38 patients who were newly diagnosed with T2DM (18 males/20 females) compared with...
a control group of 35 non-diabetic individuals (18 males/17 females). The study revealed a significantly higher level of serum resistin as compared with salivary resistin in both diabetic and control groups. It also found significantly higher levels of both serum and salivary resistin in T2DM patients as compared with the control group. Furthermore, the study revealed significant correlations between salivary resistin and BMI ($r = 0.39$), glycated haemoglobin ($r = 0.31$) and the homeostatic model assessment of IR ($r = 0.20$)[29]. Collectively, these findings along with the presence of a consistent fluctuating trend of salivary and serum resistin levels during the oral glucose tolerance test provide evidence that indicates that the source of resistin in the saliva of newly diagnosed T2DM is mainly derived from the blood[29] rather than from local production by the salivary glands[79].

The above findings are further supported by a study conducted by Sarhat et al[80] in Iraq in which a significantly higher concentration of resistin was found in the saliva of patients with T2DM as compared with a healthy control group.

In 2017, Al-Rawi and Al-Marzooq[81] undertook a study in the United Arab Emirates to assess concentrations of resistin in the saliva of 26 obese diabetics, 26 obese non-diabetics, and 26 non-obese non-diabetics. The study found no difference in resistin concentration between obese diabetics (14.7 ± 2.8 ng/mL) and obese non-diabetics (14.4 ± 3.6 ng/mL), but the concentration level in these two groups was significantly higher than in non-obese non-diabetics (10.8 ± 6.1 ng/mL, $P = 0.01$). The study also reported a significant correlation between salivary resistin and BMI. However, there was no correlation between salivary resistin and glucose level[81].

A study by Srinivasan et al[82] in 2018 in the United States assessed not only the level of resistin, but also the levels of adiponectin, visfatin, and ghrelin in unstimulated whole saliva as biomarkers for T2DM. The study involved two groups: 20 periodontally healthy patients with self-reported T2DM and a control group of 20 individuals with no known oral or systemic diseases. Salivary resistin was measured using an enzyme-linked immunosorbent assay kit. The study found that the glycated haemoglobin values of the diabetic group were consistent with the diagnosis of T2DM. It also revealed a significantly higher level of salivary resistin in the T2DM group (9.2 ± 2.3 ng/mL) as compared with the control group (5.7 ± 1.3 ng/mL). However, the study did not assess the correlation between salivary resistin and IR. Based on their findings, Srinivasan et al[82] supported the potential use of salivary resistin as a biomarker for T2DM. However, they emphasized that some caution needs to be exercised during the collection of saliva for this purpose because certain factors may affect the interpretation of the results. Specifically, they noted that it was important to consider whether the saliva is stimulated or unstimulated and to account for the existence of circadian variations. They also recommended that pre-processing of saliva should be performed in order to reduce the possibility of the presence of confounding factors such as oral or systemic diseases[82].
Table 1 Salivary resistin concentration in association with body mass index and the homeostatic model assessment of insulin resistance

| Study group          | BMI (kg/m²) | Salivary resistin (ng/mL) | Correlation with BMI | Correlation with blood glucose | Correlation with HOMA-IR | Correlation test used | Ref.                  |
|----------------------|-------------|---------------------------|----------------------|-------------------------------|-------------------------|-----------------------|-----------------------|
| Healthy              | 22.39 ± 3.65| 1.69                      | NS                   | -                             | -                       | Partial correlation   | Mamali et al[77]      |
| T2DM                 | 25.5 ± 4.9  | 3.4 ± 0.41                 | -0.391               | -0.14                         | -0.201                  | Pearson’s test        | Yin et al[29]         |
| Control              | 23.9 ± 3.3  | 1.5 ± 0.3                  | -0.17                | -0.281                        | -0.19                   |                       |                       |
| T2DM                 | -           | 4 ± 0.45                  |                     | -                             | -                       | -                     | Sarhat et al[80]      |
| Control              | -           | 1.73 ± 0.34               |                     | -                             | -                       | -                     |                       |
| Obese diabetic       | 34.3 ± 3.9  | 14.7 ± 2.8                | Significant          | NS                            | -                       |                       |                       |
| Obese non-diabetic   | 34.2 ± 2.9  | 14.4 ± 3.6                | Significant          | -                             | -                       |                       | Al-Rawi and Al-Marzooq[81] |
| Control “Non-obese-non-diabetic” | 7.1 ± 2.1 | 10.8 ± 6.1                | Significant          | -                             | -                       |                       |                       |
| T2DM                 | -           | 9.2 ± 2.3                 | -                   | -                             | -                       |                       | Srinivasan et al [82] |
| Control              | -           | 5.7 ± 1.3                 | -                   | -                             | -                       | -                     |                       |
| GDM                  | 32 (20.4-43.7) | 13.11                   | -                   | -                             | -                       | -                     | Gürlek and Çolak [83] |
| Control              | 27.2 (19.4-42) | 5.9                    | -                   | -                             | -                       | -                     |                       |

1Significant difference between the study groups, significant correlation. BMI: Body mass index; HOMA-IR: Homeostatic model assessment of insulin resistance; NS: Not significant; T2DM: Type 2 diabetes mellitus; GDM: Gestational diabetes mellitus.

More recently, in 2020, Gürlek and Çolak[83] investigated the effectiveness of evaluating salivary resistin concentrations as a screening marker for gestational diabetes mellitus (GDM). Gestational diabetes mellitus is a type of diabetes that occurs during pregnancy with an incidence that varies from 1% to 25%[84,85]. Studies have revealed that GDM is associated with decreased insulin sensitivity and release of pro-inflammatory cytokines such as resistin[86]. Also, a recent meta-analysis supported the use of serum resistin concentrations to screen for GDM[87]. Studies have also shown that the risk of GDM is far higher among overweight and obese pregnant women, especially those with central obesity[88-90]. Gürlek and Çolak[83] included 81 pregnant women in their study: 41 with newly diagnosed GDM and 40 with normal pregnancy without GDM. Fasting blood and unstimulated saliva samples were collected, and resistin was estimated using an enzyme-linked immunosorbent assay. The study revealed that pregnant women with GDM had significantly higher pre-gestational BMI, BMI at the time of sampling, and salivary resistin concentrations as compared with the pregnant women without GDM. Hence their study provided evidence for the first time that resistin concentrations in saliva might be a useful screening marker for GDM[83].

A summary of the findings related to the concentration of resistin in saliva and its correlation with BMI, homeostatic model assessment of IR, and blood glucose level are presented in Table 1.

CONCLUSION
The available evidence indicates that resistin plays a role in the development of IR. Prior studies also support the use of serum resistin as a reliable marker for IR. The evidence also supports the potential use of salivary resistin as a reliable biomarker for IR. However, the number of studies that assessed the correlation of salivary resistin with IR among obese, newly diagnosed T2DM patients is still limited.
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