Review

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Diabetes as a complication of adipose tissue dysfunction. Is there a role for potential new biomarkers?

Abstract

Increasing incidence of type 2 diabetes is a major health problem of the modern world and requires new diagnostic tools to assess early metabolic disorders, particularly insulin resistance. The link between obesity, inflammation and insulin resistance indicates the important secretory role of adipose tissue. Proinflammatory factors (cytokines, adipokines) produced by enlarged adipose tissue are related to impaired glucose metabolism. Adipokines act as paracrine factors in adipose tissue and as endocrine hormones in the liver, muscles and central nervous system. Novel adipokines secreted from adipocytes such as retinol binding protein-4 (RBP-4), vaspin, omentin, chemerin, fibroblast growth factor 21 (FGF21), adipocyte fatty acid-binding protein (A-FABP) and dipeptidyl peptidase 4 (DPP4) demonstrate pleiotropic activity and their insulin-sensitizing or enhancing insulin resistance properties have not been clearly confirmed yet. In spite of the lack of standardized automated assay methods currently available for these novel biomarkers, promising results from several studies emphasize that they might potentially be useful prognostic factors for diabetes and its complications, especially in individuals without the typical symptoms of metabolic syndrome.

Keywords: adipokines; adipose tissue; diabetes type 2; inflammation; insulin resistance; obesity.

Introduction

Diabetes is one of the most important health and socioeconomic problem of developed countries with a growing prevalence affecting more than 4% of population. While type 1 diabetes occurs most often in children and young people and is associated with an autoimmune process destroying pancreatic beta cells, type 2 diabetes mellitus (T2DM) seems to be closely related to obesity and endocrine activity of adipose tissue. The relationship between increased body weight and waist-hip ratio (WHR) and the incidence of impaired glucose tolerance, dyslipidemia (especially hypertriglyceridemia) and hypertension was first precisely described in detail in population-based studies in the early 1980s. This constellation of characteristic symptoms was defined as the metabolic syndrome (MetS) and was soon recognized as the main cause of global epidemic and cause of death due to diabetes and cardiovascular disease. Nevertheless, these reports did not fully explain the effect of adipose tissue on glucose metabolism.

The aim of this review was to present current opinions and knowledge on the potential role of novel recently identified adipose tissue derived factors in the pathogenesis of insulin resistance and diabetes. The purpose has been achieved by a review of current literature in global databases (PubMed, Ebsco), including systematic reviews, original papers and meta-analyses about evaluation of specific adipocytokines for determining the risk of insulin resistance in laboratory practice.

Proinflammatory activity of adipose tissue and impaired glucose metabolism

In the physiological state adipose tissue plays an extremely important role, including thermoregulation, protection
of internal organs, steroid hormones production etc. However, adipose tissue exhibits also a secretory capability that depends on its mass. A number of bioactive substances such as tumor necrosis factor α (TNF-α), interleukin 6 (IL-6), angiotensinogen, plasminogen activator inhibitor type 1 and non-esterified fatty acids are secreted by adipose tissue in increased concentrations whereas synthesis of adiponectin that sensitizes cells to insulin, stimulates fat oxidation in liver and muscle and inhibits hepatic glucose production is decreased in obese humans [1]. Type 2 diabetes, characterized most of all by insulin resistance, results from disturbances in insulin action and its relative deficiency. Obesity is associated with endothelial dysfunction which develops before the onset of diabetes [2]. In type 2 diabetes the development of vascular complications may be closely related to endothelial dysfunction. It seems that endothelial dysfunction in obesity may be related to insulin resistance.

Induction of insulin resistance is related to two main mechanisms: excessive lipolysis and release of free fatty acids (FFA) from enlarged adipose tissue and secretion of inflammatory factors and specific adipocytokines (Figure 1). Some of them (TNF-α, leptin, adiponectin) influence endothelium-dependent vasodilation.

FFA are captured mainly by hepatocytes and skeletal myocytes, which stimulate the accumulation of triglycerides, diacylglycerols and ceramides in cells. Those high-energy substances can be used as glucose to produce ATP, therefore an increased synthesis of acetyl-CoA and NADP is observed in mitochondria. Reactive oxygen species (ROS) synthesized during the aerobic metabolism are responsible for organelle damage. In defense against ROS, cells block the flow of energy substrates (especially glucose) by reducing the number of receptors for insulin, insulin receptor substrates (IRS-1) and glucose transporter type 4 (GLUT-4), which interferes with the proper insulin action [3].

The molecular mechanisms of insulin activity may be impaired also by the induction of chronic low-grade inflammation in adipose tissue. Adipocytes synthesize substances with chemotactic and adhesive properties, e.g., monocyte chemotactic protein-1 (MCP-1), and vascular and intercellular adhesion molecules (VCAM, ICAM), which enhance the influx of lymphocytes and monocytes. Activated macrophages and adipocytes produce large amounts of proinflammatory factors, especially TNF-α, IL-1β and IL-6. Furthermore, adipocytes are also a source of resistin, leptin, and adiponectin, which affect inflammation.

The disturbance of insulin signal transduction is associated with proinflammatory pathways of kinase/nuclear factor κB complex (IKK-β/NF-κB) and c-Jun N-terminal protein kinase 1 (JNK1). Those mechanisms are responsible for the phosphorylation of serine and threonine in substrate proteins which inhibits signal transduction by insulin receptors. Furthermore, it leads to an increased release and movement of NF-κB to the nucleus, which stimulates the expression of genes encoding proteins involved in the development of insulin resistance, including cytokines and chemokines increasing migration of inflammatory cells into adipose tissue [4]. Thus the dysfunction or loss of insulin receptors and the inability to use glucose for cellular metabolism (despite normal or elevated insulin concentrations) leads to constantly increasing hyperglycemia. The activation of IKK-β/NF-κB and JNK1 pathways can be caused by a receptor-dependent mechanism [via Toll-like receptors (TLRs) and receptors of advanced glycation end products (RAGE)] or non-receptor mechanism (related to the intracellular stress).

Increased activity of inflammatory pathways observed in obese individuals explains the high prevalence of insulin resistance and diabetes. Excessive adipose tissue (especially visceral) seems to be crucial in the pathogenesis of impaired glucose metabolism. At this point it is worth considering whether excessive visceral fat is a sufficient risk factor for diabetes. In the early 1980s the term ‘metabolically obese normal-weight’ (MONW) was
proposed to describe metabolic disorders and increased risk of T2DM and cardiovascular disease in subjects with normal or slightly elevated body mass. In the next decades several studies confirmed higher concentration of proinflammatory cytokines (TNF-α, IL-1, IL-2, IL-6) and excessive oxidative stress in MONW individuals which are predisposing factors for insulin resistance [5–7]. These data suggest that the cause of reduced insulin sensitivity may be a tendency to increased accumulation of body fat in the abdominal area, despite normal body weight and/or anthropometric measurements, which as well as in obese leads to release of inflammatory factors from adipocytes and impairs insulin signaling pathways. Results from recent studies indicate a potential role of pathological innate immune system in the pathogenesis of insulin resistance. Its excessive activity may affect hypothalamic innate immune system in the pathogenesis of insulin resistance from recent studies indicate a potential role of pathological innate immune system in the pathogenesis of insulin resistance. Its excessive activity may affect hypothalamic innate immune system in the pathogenesis of insulin resistance.

Laboratory markers of insulin resistance

Although the diagnosis of diabetes is based mainly on the increased glucose levels, hyperglycemia is not really the cause of the disease, but only a symptom. The early detection of glucose metabolism disorders is difficult and requires the use of new diagnostic tools. Evaluation of insulin resistance is possible by clinical examinations such as hyperinsulinemic euglycemic clamp, which is a ‘gold standard’ for investigating and quantifying insulin resistance or modified insulin suppression test. The complicated nature of those techniques (need to be performed in clinical conditions, potential danger of hypoglycemia) was the impulse to simplify the evaluation. The first alternative test was the Homeostatic Model Assessment (HOMA), and a more recent method is the Quantitative Insulin Sensitivity Check Index (QUICKI). Both methods use fasting insulin and glucose concentrations to assess insulin resistance and correlate reasonably with the results of euglycemic clamp. Laboratory diagnosis seems to be fast, easy and unobtrusive to the patient, however, neither clinical techniques, nor HOMA and QUICK indexes are able to assess the causes and initial metabolic abnormalities that increase the risk of developing insulin resistance and diabetes, but only demonstrate the existing reduced tissue insulin sensitivity.

Studies on the relationship between adipose tissue and insulin resistance and diabetes have prompted the search for laboratory parameters reflecting abnormalities in adipocyte metabolism and their proinflammatory potential. This issue is particularly important in an era of increasing obesity epidemic worldwide.

The inflammatory state can be measured by various laboratory tests, however, their use in assessing of insulin resistance requires fulfillment of a key criterion – they must have a high analytical sensitivity because metabolic changes occur as a result of low-grade inflammation. A number of studies describe increased number of leukocytes, increased concentration of C-reactive protein (CRP) and recently procalcitonin (PCT) and their correlation with insulin resistance in obese and T2DM patients [11–14], nevertheless these markers are not tissue-specific and may be elevated in many other diseases, including infections, injuries, cardiovascular disease etc. In recent years investigators emphasize the role of cytokines and especially adipocytokines as biomarkers of early impaired glucose metabolism and insulin resistance. These substances have different properties – some demonstrate proinflammatory activity and enhance insulin resistance, others have anti-inflammatory and insulin sensitizing effect. Significance of increased concentration of resistin, leptin, IL-6 and TNF-α or decreased levels of adiponectin and visfatin in the pathogenesis of insulin resistance and T2DM was relatively well-understood and described in many large studies [15–17].

Among newly discovered adipokines retinol binding protein-4 (RBP-4), vaspin, omentin, chemerin, fibroblast growth factor 21 (FGF21), dipeptidyl peptidase 4 (DPP4) and adipocyte fatty acid-binding protein (A-FABP) require further interest as they are associated with obesity, insulin resistance and type 2 diabetes in humans.

Retinol binding protein-4 (RBP-4)

RBP-4 belongs to the lipocalin family transporting small hydrophobic molecules and is produced mainly in the liver and mature adipocytes (20%–40%). The encoding gene is located on chromosome 10. Its role in insulin resistance is not clearly defined. RBP-4 probably induces
the expression of enzymes involved in gluconeogenesis in hepatocytes (mainly phosphoenolpyruvate carboxykinase) and impairs insulin signaling pathways in skeletal muscle. The experimental studies in mice showed significantly higher concentrations of RBP-4 in animals with insulin resistance associated with the GLUT-4 gene defect in adipose tissue [18]. Moreover, the injection of recombinant RBP-4 in healthy mice caused insulin resistance. The relationship between serum RBP-4 and obesity in humans has not been confirmed yet in population studies. A significantly higher expression of RBP-4 in obese subjects with normoglycemia and T2DM than in lean individuals and the correlation between RBP-4, glucose concentration and BMI was observed in several studies [19]. However, in the Siuta Study the correlation between serum RBP-4 and BMI values have not been found in a group of 473 Japanese with normal blood glucose [20]. The fact is, that in obese individuals concentration of RBP-4 can be reduced by weight loss, balanced diet and exercise, leading to increased insulin sensitivity [21].

**Vaspin**

Vaspin (visceral adipose tissue-derived serpin; serpin A12) is a serine protease inhibitor produced by subcutaneous and visceral adipose tissue. Vaspin is also expressed in the skin, hypothalamus, pancreatic islets, and stomach [22]. Vaspin is considered as a potential insulin-sensitizing factor, however, the regulation of serum concentrations in human obesity and type 2 diabetes is unknown and studies report inconsistent results. Its expression in adipocytes and concentration in the blood increases with BMI and is higher in obese. Youn et al. observed nearly 50% lower vaspin concentrations in both females and males with BMI <25 kg/m² compared to overweight ones (BMI 25–29.9 kg/m²) [23]. Moreover, a similar relationship was found between individuals with <20% and >20% of body fat, but there was no significant differences in serum vaspin between subjects with normal glucose tolerance and T2DM. It is worth to note that after 4 weeks of intensive exercise training vaspin concentration was increased, approximately two-fold, in subgroups of normal glucose-tolerant, impaired glucose-tolerant and type 2 diabetic subjects, despite the reduction of BMI, WHR and percent of body fat. Vaspin may have antiatherogenic effects through its potential insulin-sensitizing properties. Studies in mice have shown that recombinant vaspin injection leads to euglycemia and improves insulin sensitivity [24]. In patients with newly diagnosed T2DM short-term continuous subcutaneous insulin infusion decreased vaspin concentration in plasma and improved insulin sensitivity [25]. Auguet et al. demonstrated significantly higher vaspin mRNA expression in obese women compared to normal weight controls, but serum vaspin correlated inversely with waist circumference and serum leptin, IL-6, lipocalin-2, which points to its potential anti-inflammatory effect [26]. Those inconsistencies indicate the need for further, more detailed population studies before this analyte can be used in clinical practice.

**Omentin**

In contrast to vaspin, omentin is synthesized mainly by adipose tissue stromal cells. Recent studies showed that omentin may have protective properties against impaired glucose tolerance. Omentin increases glucose uptake by human adipocytes in vitro through enhanced protein kinase B (AKT) phosphorylation and insulin signal transduction [27]. Decreased omentin expression in adipose tissue has been observed in subjects with overweight and obesity, as well as in patients with insulin resistance, type 2 and 1 diabetes [28, 29]. Omentin correlates negatively with plasma glucose and HOMA-IR, which suggest its capability to increase insulin sensitivity. In contrast to vaspin, omentin showed a significant inverse relation with metabolic syndrome. Auguet et al. observed the significantly higher risk of MetS in patients with low omentin concentrations and its correlation with glucose and HOMA-IR values [26]. Omentin has anti-inflammatory, anti-atherogenic and antidiabetic properties but also causes vasodilation of blood vessels and attenuates CRP-induced angiogenesis [30, 31]. Based on these results omentin may be considered the second, after adiponectin, promising adipokine which regulates the insulin sensitivity, however, its clinical relevance has to be confirmed in further studies.

**Chemerin**

One of the newly discovered adipokines chemerin is also known as retinoic acid receptor responder protein 2 (RARRES2), tazarotene-induced gene 2 protein (TIG2) or RAR-responsive protein TIG2. The protein and its receptor, chemokine-like receptor-1 (CMKLR-1) are highly expressed in adipose tissue. Chemerin plays a role as a chemoattractant protein and proinflammatory factor, but is also
associated with adipocyte differentiation and stimulation of lipolysis [32]. Studies on diabetic mice showed elevated chemerin concentrations compared to controls, however, this relationship is not clearly proven in humans [33]. Probably chemerin may reduce insulin-sensitizing (GLUT-4, leptin, adiponectin) or increase insulin-resisting agents (IL-6). Significantly elevated serum chemerin concentrations were observed in patients with T2DM and cardiovascular disease compared with healthy controls (347±14 and 341±16.5 vs. 281±13 ng/mL; p<0.01) [34]. Moreover, chemerin concentration was found to be negatively correlated with omentin-1 and positively related with selected anthropometric parameters, therefore it might be linked with obesity-induced insulin resistance, diabetes and its associated disorders. Studies in non-obese normoglycemic men have revealed that fasting chemerin and leptin correlate with M-value for insulin sensitivity performed by hyperinsulinemic-euglycemic clamp method, better than its conventional surrogates like HOMA-IR and QUICKI indexes [35]. Interestingly, only the relation between M-value and chemerin remained significant after adjusting for BMI and fasting insulin (R=-0.559; p=0.016). Hence, chemerin might be used as a marker for insulin resistance in healthy individuals without typical metabolic disorders.

### Fibroblast growth factor 21 (FGF21)

Human fibroblast growth factor 21 is a circulating protein encoded by a gene located in chromosome 19 which belongs to the human FGF superfamily. It is produced mainly in the liver but also in other tissues, such as white adipose tissue, skeletal muscle and pancreas. FGF21 is supposed to play a role in glucose and lipid metabolism regulation. Its activity depends on binding receptors FGFRs and a cofactor β-Klotho expressed in adipocytes [36]. FGF21 stimulates glucose uptake in differentiated adipocytes via the induction of glucose transporter-1 (GLUT-1), therefore may reduce blood glucose levels. However, glucose entry into adipocytes results in its storage as triglycerides and stimulates lipolysis. Released fatty acids trigger gluconeogenesis and ketogenesis in the liver, which elevates blood glucose and leads to insulin resistance. Increased concentrations of serum FGF21 have been found in obese children and adults [37, 38]. Interestingly, several studies have shown paradoxically elevated FGF21 expression after a short-term very low calorie diet [39], thus its production seems to be independently regulated by fasting and feeding signals and increase both in starvation and overfeeding. Recent studies suggest significant correlation between FGF21 and BMI, TG, insulin, low HDL-cholesterol and impaired glucose tolerance, therefore it might be an independent risk factor for insulin resistance, T2DM and MetS [40, 41]. Cuevas-Ramos et al. observed that hyperglycemia, elevated BMI and uric acid levels and low physical activity are independent factors influencing serum FGF21 [42]. In the 5 years follow-up study high levels of FGF21 predicted impaired glucose metabolism (OR=2.2; 95% CI 1.3–3.6; p=0.002), metabolic syndrome (OR=2.6; 95% CI 1.5–4.5; p=0.001) and T2DM (OR=2.4; 95% CI 1.2–4.7; p=0.01) after adjustment for age, sex and BMI [41]. Interestingly, in men FGF21 was linked with enhanced glucose uptake in skeletal muscles and inhibition of lipolysis in adipocytes, probably as a compensatory mechanism [43].

### Dipeptidyl peptidase 4 (DPP4)

Dipeptidyl peptidase 4 is a transmembrane glycoprotein enzyme which cleaves N-terminal dipeptides from a variety of substrates (growth factors, hormones, chemokines). One of the most important biological activities of DPP4 is hydrolysis and inactivation of gastrointestinal hormones: glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotrophic peptide (GIP) that are released from the intestinal mucosa and responsible for approximately 60% of postprandial insulin secretion [44]. As GLP-1 is a potent antihyperglycemic hormone, DPP4 inhibitors are promising oral hypoglycemic and insulin-sensitizing drugs used in T2DM [45]. Although there is a lack of conclusive data demonstrating proinflammatory properties of DPP4, several studies showed anti-inflammatory effects of DPP4 inhibitors in patients with diabetes and cardiovascular disease [46, 47]. Lamers et al. evaluated the relationship between DPP4 and metabolic syndrome in two independent studies [48]. They found that DPP4 is expressed in differentiated adipocytes and decreases insulin action in both adipocytes and muscle cells. Moreover, in vitro study has proven that DPP4 expression in obese individuals is higher in visceral than in subcutaneous fat tissue. Serum DPP4 was significantly elevated in obese compared to lean subjects and correlated with insulin resistance factors, like visceral adipocyte surface (R=0.40; p=0.02), adiponectin (R=-0.37; p=0.03), leptin (R=0.46; p=0.005) and HOMA-IR (R=0.63; p<0.001) and also with components of metabolic syndrome (BMI, TG, HDL-C). DPP4 activity may be regulated by weight loss. Studies in obese children have shown the relation between changes of DPP4 activity with decrease of percentage body fat [49]. Enzyme activity was also negatively correlated with pancreatic peptide
(PP) and peptide YY (PYY) concentrations, which have potent anti-obesity properties.

**Adipocyte fatty acid binding protein (A-FABP)**

A-FABP is one of the fatty acid-binding proteins isoforms which is expressed mainly in adipose tissue and macrophages. Its biological activity refers to binding hydrophobic ligands such as long chain fatty acids and facilitating their transport to specific cell compartments [50]. Therefore, this protein is involved in lipid and glucose homeostasis. Hui et al. reported that A-FABP might have proinflammatory properties related to lipopolysaccharide-induced inflammation by forming a positive feedback loop with the JNK/c-Jun signaling cascade [51], which is involved in impaired insulin action. Several studies showed correlation between A-FABP and proinflammatory factors, like CRP and their similar importance in predicting insulin resistance [52, 53]. A number of studies confirmed significantly higher concentration of A-FABP in overweight/obese individuals and its relationship with obesity, metabolic syndrome and insulin resistance in both lean and obese subjects [54–56]. A-FABP is an independent predictor for development of MetS in non-diabetic subjects during the 5-year follow-up, adjusted for HOMA-IR and BMI (OR=4.7; 95% CI 1.8–11.9; p=0.001) [57]. In clinically healthy Korean boys A-FABP compared to adiponectin and RBP-4, was the only independent predictor of metabolic syndrome development after adjustment for insulin resistance, BMI, sleep duration and physical activity (OR=17.3; 95% CI 1.25–239.7; p<0.05) [58]. Interestingly, A-FABP concentration in obese individuals decreases significantly after bariatric surgery and intensive weight loss, which improves insulin sensitivity. However, some data suggest A-FABP has similar properties to FGF21 and tends to increase in both overfeeding and starvation [59, 60].

**Novel biomarkers in laboratory practice – new opportunities, constant issues**

Increasing incidence of type 2 diabetes and earlier appearance of glucose metabolism disturbances require constant search for new risk assessment strategies. In recent years much attention is paid to the ‘omics’ methods whereby it is possible to determine the molecular basis of many pathologies. Isolation and identification of adipose-derived proteins involved in insulin resistance is a major goal of proteomics. In addition, the spatial structure and interdependencies between proteins can be resolved. These methods, utilizing advanced technologies such as liquid chromatography and mass spectrometry allowed the identification of over 80 proteins expressed in adipocytes, the properties of which can contribute to the development of civilization diseases [61]. Proteomic studies are closely related to metabolomics. Detailed analysis of metabolic pathways and various metabolites enable the evaluation of the impairment of certain biochemical reactions and signaling pathways which determine insulin resistance. Recent studies focus on metabolites such as acylcarnitines, amino acids, hexose, and phospholipids in the serum [62, 63]. Of these, glycine, sphingomyelin, acyl-alkylphosphatidylcholines and lysophosphatidylcholine (LPC 18:2) were independently associated with decreased risk whereas hexose, phenylalanine and diacyl-phosphatidylcholines with increased risk of T2DM. Last but not least, the way of searching for new biomarkers of insulin resistance is genomics which allows the analysis of genes involved in the expression of different proteins, enzymes, receptors etc. related to glucose metabolism. Interesting results from genome-wide association studies (GWAS) led to the discovery of 38 SNPs and illustrated many pathways associated with insulin resistance and T2DM,

<table>
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<th>Authors</th>
<th>Diagnosis</th>
<th>Cut-off</th>
<th>Sensitivity</th>
<th>Specificity</th>
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<td>Shim et al. [33]</td>
<td>insulin resistance</td>
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<td>53.9%</td>
<td>60.6%</td>
</tr>
<tr>
<td>Maghbooli et al. [34]</td>
<td>risk of GDM</td>
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<td>65.3%</td>
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<td>Vaspin</td>
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<tr>
<td>Cakal et al. [35]</td>
<td>diabetes risk in PCOS females</td>
<td>1.82 ng/mL</td>
<td>83.3%</td>
<td>66.1%</td>
</tr>
<tr>
<td>Chemerin</td>
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<td>95 ng/mL</td>
<td>75%</td>
<td>80%</td>
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<tr>
<td>Osman et al. [65]</td>
<td>metabolic syndrome</td>
<td>16.4 μg/L</td>
<td>40%</td>
<td>99%</td>
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Table 1 Diagnostic performance of novel adipocytokines in evaluating the risk of insulin resistance or diabetes.

GDM, gestational diabetes mellitus; PCOS, polycystic ovary syndrome.
e.g., a missense mutation rs13266634 in SLC30A8 gene encoding zinc transporter (ZnT-8) or HNF1A (hepatocyte nuclear factor 1-α) variants associated with type 2 diabetes, CRP and atherogenic lipid profile [64]. Despite the development of new techniques and promising results of clinical trials, the use of new biomarkers in routine diagnosis is not easy. An ideal biomarker should meet several essential criteria: be easy to measure, provide valuable information about presence/absence of disease (high diagnostic specificity and sensitivity, good reproducibility and precision), and have a good cost-effectiveness ratio. The determination of adipokines seems to be the easiest and most accessible method for the use of novel biomarkers, however, does not fulfill all the requirements. The main limitation for the use of described adipocytokines as new potential biomarkers to evaluate insulin resistance is the lack of standardization of available assay methods and still unsatisfactory diagnostic sensitivity and specificity (Table 1). For most adipokines, the data on the diagnostic value and the cut-off points for metabolic disorders are missing. Another issue is the inaccessibility of automated assay methods. Adipocytokines are mainly determined by manual immunoassays (ELISA), which are high workload and time consuming methods. Therefore, their implementation into routine laboratory menu will be possible only in the near future.

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