Endocr (2009) 36:397–403
DOI 10.1007/s12020-009-9234-7

ORIGINAL ARTICLE

Role of adipocytokines in predicting the development of diabetes and its late complications

Nese Ersoz Gulcelik · Aydan Usman · Alper Gürlek

Received: 1 June 2009 / Accepted: 31 July 2009 / Published online: 25 September 2009

Abstract Diabetes is an important health problem since the incidence of diabetes is continuously increasing. Early diagnosis is important as type 2 diabetes begins long before we diagnose it, leading to a complicated course of the disease. In order to prevent delay in the diagnosis of type 2 diabetes, novel predictors and pathways for type 2 diabetes are mounting. Diabetic complications are common cause of morbidity and mortality among subjects with diabetes. In the pathogenesis of diabetic complications some factors other than chronic hyperglycemia may be involved. Adipocytokines play important roles in the pathogenesis of diabetes mellitus, insulin resistance, and associated metabolic conditions such as hypertension and dyslipidemia. The investigations on the role of adipocytokines in developing diabetes and its complications have been made. In this review, we discussed the implications of adipocytokines in predicting diabetes and diabetic complications, with particular attention on the roles of adiponectin, leptin, visfatin, and vaspin.

Keywords Adipocytokines · Diabetes mellitus · Adiponectin · Leptin · Visfatin · Vaspin · Complications

Introduction

Adipose tissue has shown to be an active metabolic organ secreting adipocytokines. Adipocytokines are involved in the energy homeostasis and regulation of glucose and lipid metabolism, immunity and, neuroendocrine and cardiovascular function. Adipocytokines include several novel and highly active molecules released abundantly by adipocytes such as leptin, adiponectin, visfatin, and vaspin.

As the incidence of diabetes is continuously increasing, diabetes has become an important health problem. The pathogenesis of diabetes and its complications are of great interest; novel predictors and pathways for type 2 diabetes are mounting. It has been stated for years that insulin resistance is the core of the problems leading to type 2 diabetes, hypertension, and dyslipidemia. Endothelial dysfunction develops as a result of hyperglycemia and accompanying metabolic abnormalities. Hyperglycemia and hyperlipidemia have been shown to induce proinflammatory cytokines. Diabetic ketoacidosis and non-ketotic hyperglycemia were found to be associated with elevation of proinflammatory cytokines, reactive oxygen species (ROS), and cardiovascular risk factors in the absence of obvious infection or cardiovascular pathology [1]. In recent years, an alternative perspective has been suggested as endothelial dysfunction is the core element in the pathogenesis of diabetes [2–4]. Diverse molecules related to inflammation play an important role in the development of diabetes and diabetic complications. Several studies have shown a relationship between inflammatory markers and insulin resistance in diabetic, prediabetic, and non-diabetic populations [2, 5–9]. Chronic low grade inflammation has a role in the development of type 2 diabetes, and patients with diabetes have elevated levels of inflammatory markers [9–12].

Diabetic complications are a common cause of morbidity and mortality among subjects with diabetes. Chronic hyperglycemia is the main pathogenic factor involved in complications. Hyperglycemia increases factors such as polyol pathway flux, protein kinase C (PKC) activity, the production of advanced glycation end products (AGE), ROS, and thereby microvascular complications [13]. However, some factors other than glycemic control might be

N. E. Gulcelik · A. Usman · A. Gürlek (✉)
Department of Endocrinology and Metabolism, Hacettepe University Medical School, Sıhhıye, Ankara, Turkey
e-mail: agurlek2001@yahoo.com

involved in the pathogenesis of diabetic complications. Cardiovascular risk factors are associated with insulin resistance and in turn, insulin resistance is associated with the presence of microvascular complications [5, 6, 10]. There is increasing evidence that some inflammatory proteins may participate in the pathogenesis of insulin resistance and diabetic complications [14, 15]. In addition, some inflammatory markers have been associated with the presence of diabetic retinopathy, neuropathy, and nephropathy [16, 17].

The present review focuses on the effects of major adipocytokines, with particular attention on the roles of leptin, adiponectin, vaspin, and visfatin on the prediction of diabetes and its late complications. Published literature was analyzed with the intent of addressing the role of the major adipose secretory proteins in type 2 diabetes and diabetic complications.

Adiponectin

Adiponectin is the most abundantly expressed adipokine and differs from the other adipocytokines in that its concentrations decrease with increasing obesity and increases with weight loss [18, 19]. Adiponectin has been suggested to have insulin sensitizing, anti-inflammatory, and anti-atherogenic effects [20, 21]. The actions of adiponectin in suppressing gluconeogenesis and enhancing lipid oxidation are related to activation of AMP-activated protein kinase (AMPK) and inhibition of acetyl CoA carboxylase in the liver and muscle [22]. Adiponectin increases fatty-acid combustion and energy consumption and decreases tissue triglyceride content in muscle and liver. By these mechanisms, adiponectin contributes to improved insulin signal transduction and hence improved insulin sensitivity [23, 24].

Plasma adiponectin concentrations have been shown to correlate strongly with insulin sensitivity [25–27] which suggests that low plasma concentrations are associated with insulin resistance. Furthermore, as direct evidence, several previous reports including ours have demonstrated the inverse correlation between adiponectin levels and insulin resistance in diverse patient populations such as type 2 diabetes and polycystic ovary syndrome [28–32]. Plasma concentrations of adiponectin are lower in patients with type 2 diabetes. Pima Indians with high adiponectin levels are less likely to develop type 2 diabetes than those with low concentrations of adiponectin [33]. It was found that the relationship of markers of subclinical inflammation to the development of type 2 diabetes is mediated by adiponectin in Pima Indians. Adiponectin, while having anti-inflammatory activity, may mediate diabetes risk via mechanisms other than inflammation [34]. Low concentrations of adiponectin predicted subsequent development of IGT and type 2 diabetes in normoglycemic middle-aged Finnish subjects, suggesting that adiponectin may play a role in the pathogenesis of abnormal glucose metabolism [35]. A prospective study of 1038 healthy women revealed that adiponectin is strongly and inversely associated with risk for diabetes independent of body mass index, whereas resistin did not [36]. Adiponectin is, therefore, a predictive marker for the development of type 2 diabetes. The ratio of high-molecular-weight (HMW) to total adiponectin is related to risk for diabetes independent of total adiponectin, suggesting an important role of the relative proportion of HMW adiponectin in diabetes pathogenesis [36]. Any factor interfering with glucose metabolism may cause type 2 diabetes. Hypoadiponectinemia seems to be one of the important factors in the pathogenesis of diabetes.

Insulin resistance of type 2 diabetes is closely associated with the progression of microangiopathies leading retinopathy, nephropathy, and neuropathy [37]. Adiponectin improves insulin sensitivity and hyperglycemia and, therefore, could affect the development and/or progression of diabetic microangiopathy. However, the relationship between diabetic microangiopathies and serum total adiponectin is controversial. Yilmaz et al. [38] found that plasma adiponectin concentrations in patients with proliferative diabetic retinopathy or non-proliferative diabetic retinopathy were significantly lower than those in patients without diabetic retinopathy; and adiponectin levels were negatively correlated with the severity of proteinuria in diabetic patients [39]. Lin et al. [40] suggested that higher serum adiponectin concentration is associated with reduced odds of moderate renal dysfunction in men with type 2 diabetes. Contrary to these findings, some researchers found increased levels of adiponectin in patients with nephropathy and retinopathy [41–44]. Kato et al. showed that serum total and HMW adiponectin levels appear to be increasing in T2DM subjects at an advanced stage of diabetic retinopathy and nephropathy, but not in those with neuropathy [28]. No association has been found between adiponectin levels and diabetic neuropathy in two different studies [45, 46]. The absence of a relationship between neuropathy and adiponectin may be explained by the fact that mechanisms other than those involving the vasculature are also implicated in its pathogenesis. Furthermore, under diagnosing the neuropathies in some patients might have led to find no association between them.

As the kidney is an important elimination site for circulating adiponectin, impaired renal clearance is thought to contribute to the elevated levels of adiponectin in diabetic patients with advanced nephropathy. However, it has been reported in type 2 diabetic patients with different stages of nephropathy that urinary adiponectin levels are markedly higher in subjects with macroalbuminuria than those with normoalbuminuria and microalbuminuria [47]. Serum adiponectin levels are also significantly elevated in patients

with macroalbuminuria compared to the ones with normoalbuminuria [47]. Increased adiponectin levels may not be related to decreased elimination in patients with nephropathy. Rather than decreased elimination of adiponectin, endothelial dysfunction may itself result in a compensatory increase in adiponectin levels to overcome microangiopathy. Whether increased adiponectin protects the individual from microangiopathy or increased levels are due to ineffectiveness of circulating adiponectin needs to be further determined.

Age, gender, and race are needed to be considered while interpreting the adiponectin levels. Despite the increase in visceral fat and insulin resistance with normal aging, adiponectin levels are known to increase with age. Adiponectin levels were found to be increased in female subjects, indicating a sex hormone affect on circulating adiponectin levels [48]. Race has also shown to have an effect on adiponectin levels. Kanaya et al. [49] have shown that older white Americans had higher median serum levels of total adiponectin compared with older Blacks. Adiponectin was independently associated with a higher prevalence and incidence of coronary heart disease among Black subjects, but this effect was attenuated by glucose tolerance, HDL-cholesterol, fasting insulin concentrations, and CRP in White subjects.

There are points that need to be clarified in adiponectin's role in diabetes and its micro- and macrovascular complications. Adiponectin seems to be beneficial in case of insulin resistance and diabetes as a prediction marker, and seems to have a role in the pathogenesis of diabetes. However, this issue is complicated in case of diabetic micro- and macrovascular complications. Higher levels protect the individual from diabetes but may also serve as a poor prognostic factor for nephropathy and retinopathy.

Leptin

Leptin is a 167 amino acid hormone secreted largely by adipose tissue [50]. Plasma leptin level and mRNA expression is directly related to obesity. The absence of leptin or a mutation in the leptin receptor gene induces hyperphagia and obesity in animal models as well as in humans [51–53]. However, in obese humans, generally high leptin levels are determined suggesting leptin resistance and, hence, leptin administration has not proven to be successful [54]. Leptin has shown to be associated with insulin resistance and inflammatory factors [55]. In type 2 diabetes mellitus hyperinsulinemia has been reported to associate with elevated leptin levels independent of body fat mass [56]. Serum leptin levels were found to be decreased in lean and obese patients with diabetic ketoacidosis or hyperglycemia and, low serum leptin levels were attributed to impaired adipocyte glucose utilization due to insulin deficiency and/or to increased cathecolamine levels. Insulin treatment resulted in a rapid and significant increase in leptin levels in these patients [57, 58]. Leptin directly regulates insulin sensitivity and pancreatic ß cell function. Since leptin has a restraining effect on normal insulin secretion by the pancreas, leptin resistance might occur in β-cells of obese individuals adding to their hyperinsulinaemia. Moreover, anti-apoptotic effects of leptin in β-cells could be diminished in a leptin-resistant state [59]. Leptin levels were found to be higher in female diabetic and non-diabetic patients than the male patients [60, 61]. So far the association of leptin with risk of developing diabetes has remained unclear. The ARIC study, which investigated the effect of leptin levels on predicting diabetes adjusting for age, sex, ethnicity, and study center, suggested that high leptin levels, probably reflecting leptin resistance, predict an increased risk of diabetes [61]. Conversely, some authors have failed to find an association with increased odds of diabetes [62]. Leptin is primarily metabolized by the kidneys—filtered by glomeruli and reabsorbed by the proximal convoluted tubules via megalin-mediated endocytosis [63]. The leptin receptor is shown to be expressed on the proximal straight tubules, loops of Henle, distal tubules, and collecting ducts [63]. It is likely that leptin accumulates in proximal tubuli cells of individuals with hyperleptinemia in which it undergoes degradation [64]. However, excess leptin molecules may act via the leptin receptor on the other downstream tubule cells. Alternatively, some leptin molecules may be involved in pathological signal transduction in proximal tubule cell, possibly via megalin. Evidence is accumulating that diabetic nephropathy is associated with metabolic overload of nephrotoxic proteins or proteins with nephrotoxic ligands in proximal tubule cell via megalin-mediated endocytosis [63, 64]. Fruehwald-Schultes et al. have shown that leptin levels are elevated in a small group of diabetic patients with microalbuminuria [65]. Conversely, Asakawa et al. [66] found that the leptin level was not elevated in subjects with microalbuminuria. A link between the existence of diabetic retinopathy and serum leptin levels in type 2 diabetes has been shown, but not confirmed, in type 1 and type 2 diabetes [67–69]. With regard to neuropathy, serum leptin was shown to be higher in women with parasympathetic neuropathy than in those without this complication [70]. Doupis et al. [71] have recently shown that leptin levels are increased in patients with diabetic neuropathy compared to non-neuropathic diabetic patients and healthy controls. However, Matsuda et al. [69] could not find an association between leptin levels and diabetic neuropathy. Taken together, these data suggest that the implication of leptin in neuropathic diabetic complications is questionable, and there are data indirectly showing that leptin may be involved in the development of neuropathy.

At present, the value of leptin in predicting diabetes is unclear. Although some authors have suggested that high leptin levels, probably reflecting leptin resistance, predict an increased risk of diabetes; others have failed to confirm this finding. The results of the studies on the association of leptin with diabetic complications are controversial and needs further investigation.

Visfatin

Visfatin is a novel adipokine produced mainly in the visceral fat of both humans and mice. Several clinical studies were conducted in order to analyze the validity of visfatin data and its relationship with insulin resistance, diabetes, and obesity. However, there are controversies in the results of these studies [72–80]. Plasma visfatin levels are increased in obese patients and decreased with weight loss [72]. Chen et al. [73] have found that plasma visfatin levels are increased and positively correlated with waist-to-hip ratio in type 2 diabetes. Other investigators have also found increased levels of visfatin in type 2 diabetic patients but failed to find a correlation between anthropometric measurements, lipid measures, fasting glucose, insulin resistance (HOMA-IR), and beta-cell function (HOMA-B). Furthermore, two different studies have failed to find a correlation between visfatin levels and markers of insulin sensitivity [79, 80]. Visfatin/PBEF gene polymorphisms have been found to be related to the risk of type 2 diabetes. This effect was suggested to be mediated by the pro-inflammatory actions of this molecule [81]. However, another genetic study of visfatin concluded that the variants tested did not play a major role in obesity or type 2 diabetes but may have a minor contribution in determining glucose homeostasis and visfatin mRNA expression [82]. In a study investigating visfatin levels in type 2 diabetic patients, patients with impaired glucose tolerance and normal blood glucose; visfatin levels were higher in patients with type 2 diabetes than the other groups. There was no difference in visfatin levels between patients with impaired glucose tolerance and the control group [76]. Thus, the role of visfatin in predicting diabetes is still unclear.

There are major inconsistencies and limitations in the detection of serum visfatin levels by different immunoassays [83]. This needs to be considered when interpreting data from clinical studies, and it may in part explain the controversial observations on the relation of circulating visfatin to diabetes. Race also seems to have an affect on serum visfatin levels. Serum visfatin levels are associated with visceral adiposity and type 2 diabetes in Asian people; however, studies in Europe could not confirm this association [71, 79].

Implication of visfatin in diabetic nephropathy has been studied in two studies. Song et al. [84] have observed that visfatin was synthesized in mesangial cells as well as adipocytes and increased by high glucose stimuli which contributes to increased glucose influx into mesangial cells, thereby, accelerating diabetic nephropathy through the aggravation of metabolic alterations. Yilmaz et al. [85] have suggested that the presence of proteinuria, regardless of the degree of renal functional impairment, is an important predictor of endothelial dysfunction in early diabetic nephropathy. This condition is associated with altered circulating levels of visfatin and adiponectin [85]. Visfatin seems to be involved in the pathogenesis of diabetic nephropathy since it is synthesized by the mesangial cells and has a role in endothelial dysfunction.

Although the role of visfatin in predicting diabetes is unclear; its role in the pathogenesis of diabetic nephropathy is inspiring. Visfatin synthesis from mesangial cells increases under high glucose conditions and accelerates diabetic nephropathy. Hyperglycemia, not only by glucotoxicity but also by increasing visfatin levels, may lead to diabetic nephropathy which is a promising finding to prevent diabetic complications by sustaining normoglycemia and decreasing visfatin levels.

Vaspin

Vaspin is a novel adipocytokine identified by Hida et al. as a member of the serine protease inhibitor family and expressed in visceral adipose tissue of Otsuka Long-Evans Tokushima Fatty (OLETF) rats, which is an animal model of abdominal obesity and type 2 diabetes mellitus. Vaspin has been suggested as a compensatory factor against the insulin resistant state of metabolic syndrome in cross-sectional expression studies from both human visceral and subdermal white adipose tissue samples [86, 87]. In OLETF rats, serum vaspin levels peaked at the age when obesity and insulin plasma concentrations reach a peak; however, vaspin levels decrease with the worsening of diabetes and weight loss [86].

A few studies have been reported regarding serum vaspin levels and vaspin expression in fat tissue in humans, and the correlation between vaspin serum levels and markers of insulin sensitivity and glucose metabolism are unclear [88–91]. Klöting et al. [88] have suggested that human vaspin mRNA expression in adipose tissue is regulated in a fat depot-specific manner and could be associated with parameters of obesity, insulin resistance, and glucose metabolism. A study investigating the association of vaspin single nucleotide polymorphisms with type 2 diabetes and obesity demonstrated a significant association with type 2 diabetes independent of obesity [92]. However, Seeger et al. [89] have failed to find a correlation between vaspin levels and markers of insulin sensitivity and glucose metabolism in chronic hemodialysis patients and control subjects including those with diabetes. Youn et al. [90], in

a cross-sectional study of 187 subjects with diabetes mellitus, impaired glucose tolerance, or normal glucose tolerance, have found an association between vaspin serum levels, BMI and insulin sensitivity, but could not confirm this correlation in patients with type 2 diabetes. We have recently found an association between serum vaspin levels and insulin resistance in diabetic women and a positive correlation of serum vaspin levels with glycosylated hemoglobin [93]. An interesting finding established by Tan et al. and confirmed by us is that metformin treatment lowers serum vaspin levels [93, 94]. We have also found that patients with microvascular complications have lower serum vaspin levels than those without microvascular complications [93]. Further investigations as to whether this finding is due to a vascular impairment or a consequence of other factors that leads to the worsening of the diabetic condition may reveal this issue. However, we can speculate that the defensive mechanism of vaspin might be ceased by the development of microvascular complications. The identification of a protease substrate for the induction of vaspin may clarify the role of vaspin in diabetes and microvascular complications of diabetes.

Conclusions

The role of the mentioned adipokines in the development of diabetes is not exactly known at the present time. Whether they play a direct role in the pathogenesis of diabetes, or they are only initial suggestive markers of diabetes is unclear. In case of both conditions, however, they may help us determine the patients at risk in an attempt to prevent or delay the development of diabetes. Some adipokines are shown not to be useful in predicting diabetes due to alterations in their secretion and function with the progression of the prediabetic state. In case of late complications of diabetes, adipokine level determinations seem even less useful. Rather than the presence of nephropathy, retinopathy or neuropathy, the common pathogenetic conditions seem to lead to alterations in their levels. Selected adipokines like adiponectin may be helpful in predicting diabetes. Although alterations in levels of adipokines may be seen in the presence of late complications of diabetes, their value in the diagnosis and potential management of these complications is still questionable.

References

1. F.B. Stentz, E.G. Umpierrez, R. Cuervo, A.E. Kitabchi, Diabetes **53**, 2079–2086 (2004)
2. J.C. Pickup, Diabetes Care **27**, 813–823 (2004)
3. J.H. Pinkney, C.D. Stehouwer, S.W. Coppack, J.S. Yudkin, Diabetes **46**, S9–S13 (1997)
4. J.C. Pickup, M.B. Mattock, G.D. Chusney, D. Burt, Diabetologia **40**, 1286–1292 (1997)
5. A. Festa, R. D'Agostino, G. Howard, L. Mykkänen, R.P. Tracy, S.M. Haffner, Circulation **101**, 42–47 (2000)
6. J.F. Navarro, C. Mora, Nephrol. Dial. Transplant. **20**, 2601–2604 (2005)
7. E.S. Ford, Diabetes **22**, 1971–1977 (1999)
8. S. Müller, S. Martin, W. Koenig et al., Diabetologia **45**, 805–812 (2002)
9. T. Temelkova-Kurktschiev, E. Henkel, C. Koelher, K. Karrei, M. Hanefeld, Diabetologia **45**, 151 (2002)
10. J. Pickup, M. Crook, Diabetologia **41**, 1241–1248 (1998)
11. J.F. Navarro, C. Mora, M. Macía, J. García, Am. J. Kidney Dis. **42**, 53–61 (2003)
12. J.C. Pickup, G.C. Chusney, S.M. Thomas, D. Burt, Life Sci. **67**, 291–300 (2000)
13. J.G. Mabley, F.G. Soriano, Curr. Vasc. Pharmacol. **3**, 247–252 (2005)
14. J.M. Fernandez-Real, W. Ricart, Endocr. Rev. **24**, 278–301 (2003)
15. P.A. Tataranni, E. Ortega, Diabetes **54**, 917–927 (2005)
16. G. Zoppini, G. Faccini, M. Muggeo, L. Zenari, G. Falezza, G. Targher, J. Clin. Endocrinol. Metab. **86**, 3805–3808 (2001)
17. M.T. Schram, N. Chaturvedi, C.G. Schalkwijk, J.H. Fuller, C.D. Stehouwer, Diabetologia **48**, 370–378 (2005)
18. Y. Arita, S. Kihara, N. Ouchi, M. Takahashi, K. Maeda, J. Miyagawa, K. Hotta, I. Shimomura, T. Nakamura, K. Miyaoka, H. Kuriyama, M. Nishida, S. Yamashita, K. Okubo, K. Matsubara, M. Muraguchi, Y. Ohmoto, T. Funahashi, Y. Matsuzawa, Biochem. Biophys. Res. Commun. **257**, 79–83 (1999)
19. W.S. Yang, W.J. Lee, T. Funahashi, S. Tanaka, Y. Matsuzawa, C.L. Chao, C.L. Chen, T.Y. Tai, L.M. Chuang, J. Clin. Endocrinol. Metab. **86**, 3815–3819 (2001)
20. O. Ukkola, M. Santaniemi, J. Mol. Med. **80**, 696–702 (2002)
21. J. Hulte, L.M. Hulten, B. Fagerberg, Metabolism **52**, 1612–1614 (2003)
22. T. Yamauchi, J. Kamon, Y. Minokoshi, Y. Ito, H. Waki, S. Uchida, S. Yamashita, M. Noda, S. Kita, K. Ueki, K. Eto, Y. Akanuma, P. Froguel, F. Foufelle, P. Ferre, D. Carling, S. Kimura, R. Nagai, B.B. Kahn, T. Kadowaki, Nat. Med. **8**, 1288–1295 (2002)
23. T. Yamauchi, K. Hara, N. Kubota, Y. Terauchi, K. Tobe, P. Froguel, R. Nagai, T. Kadowaki, Curr. Drug Targets Immune Endocr. Metab. Disord. **3**, 243–254 (2003)
24. T. Yamauchi, J. Kamon, H. Waki, Y. Terauchi, N. Kubota, K. Hara, Y. Mori, T. Ide, K. Murakami, N. Tsuboyama-Kasaoka, O. Ezaki, Y. Akanuma, O. Gavrilova, C. Vinson, M.L. Reitman, H. Kagechika, K. Shudo, M. Yoda, Y. Nakano, K. Tobe, R. Nagai, S. Kimura, M. Tomita, P. Froguel, T. Kadowaki, Nat. Med. **7**, 941–946 (2001)
25. N. Steafan, B. Vozarova, T. Funahashi, Y. Matsuzawa, C. Weyer, R.S. Lindsay, J.F. Youngren, P.J. Havel, R.E. Pratley, C. Bogardus, P.A. Tataranni, Diabetes **51**, 1884–1888 (2002)
26. N. Maeda, I. Shimomura, K. Kishida, H. Nishizawa, M. Matsuda, H. Nagaretani, N. Furuyama, H. Kondo, M. Takahashi, Y. Arita, R. Komuro, N. Ouchi, S. Kihara, Y. Tochino, K. Okutomi, M. Horie, S. Takeda, T. Aoyama, T. Funahashi, Y. Matsuzawa, Nat. Med. **8**, 731–737 (2002)
27. N. Ouchi, S. Kihara, Y. Arita, Y. Okamato, K. Maeda, H. Kurihara, Circulation **102**, 1296–1301 (2000)
28. O. Tschritter, A. Fritsche, C. Thamer, M. Haap, F. Shirkavand, S. Rah, H. Staiger, E. Maerker, H. Häring, M. Stumvoll, Diabetes **52**, 239–243 (2003)
29. M.F. Hivert, L.M. Sullivan, C.S. Fox, D.M. Nathan, R.B. D'Agostino, P.W. Wilson, J.B. Meigs, J. Clin. Endocrinol. Metab. **93**(8), 3165–3172 (2008)

30. C. Weyer, T. Funahashi, S. Tanaka, K. Hotta, Y. Matsuzawa, R.E. Pratley, P.A. Tataranni, J. Clin. Endocrinol. Metab. **86**, 1930–1935 (2001)
31. J. Spranger, M. Möhlig, U. Wegewitz, M. Ristow, A.F. Pfeiffer, T. Schill, H.W. Schlösser, G. Brabant, C. Schöfl, Clin. Endocrinol. (Oxf) **61**, 738–746 (2004)
32. N.E. Gulcelik, Y. Aral, R. Serter, Y. Demir, C. Culha, Gynecol. Endocrinol. **22**, 511–515 (2006)
33. R.S. Lindsay, T. Funahashi, R.L. Hanson, Y. Matsuzawa, S. Tanaka, P.A. Tataranni, W.C. Knowler, J. Krakoff, Lancet **360**, 57–58 (2002)
34. J. Krakoff, T. Funahashi, C.D. Stehouwer, C.G. Schalkwijk, S. Tanaka, Y. Matsuzawa, S. Kobes, P.A. Tataranni, R.L. Hanson, W.C. Knowler, R.S. Lindsay, Diabetes Care **26**(6), 1745–1751 (2003). Jun
35. K. Jalovaara, M. Santaniemi, M. Timonen, J. Jokelainen, Y.A. Kesäniemi, O. Ukkola, S. Keinänen-Kiukaanniemi, U. Rajala, Metabolism **57**, 1130–1134 (2008)
36. C. Heidemann, Q. Sun, R.M. van Dam, J.B. Meigs, C. Zhang, S.S. Tworoger, C.S. Mantzoros, F.B. Hu, Ann. Intern. Med. **149**, 307–316 (2008)
37. M. Suzuki, A. Kanazawa, M. Shiba, H. Kojima, Y. Harano, J. Diabetes Complicat. **14**, 40–45 (2000)
38. M.I. Yilmaz, A. Sonmez, C. Acikel, T. Celik, N. Bingol, M. Pinar, Z. Bayraktar, M. Ozata, Eur. J. Endocrinol. **151**, 135–140 (2004)
39. M. Yenicesu, M.I. Yilmaz, K. Caglar, A. Sonmez, T. Eyileten, T. Kir, C. Acikel, N. Bingol, Y. Oguz, T.A. Ikizler, A. Vural, Clin. Nephrol. **64**, 12–19 (2005)
40. J. Lin, F.B. Hu, G. Curhan, Diabetes Care **30**, 239–244 (2007)
41. B. Zietz, C. Buechler, K. Kobuch, M. Neumeier, J. Schölmerich, A. Schäffler, Exp. Clin. Endocrinol. Diabetes **116**, 532–536 (2008)
42. T. Saito, O. Saito, T. Kawano, H. Tamemoto, E. Kusano, M. Kawakami, S.E. Ishikawa, Diabetes Res. Clin. Pract. **78**, 85–92 (2007)
43. H. Komaba, N. Igaki, S. Goto, K. Yokota, H. Doi, T. Takemoto, M. Kohno, Y. Hirosue, T. Goto, Am. J. Nephrol. **26**, 476–482 (2006)
44. H.C. Looker, J. Krakoff, T. Funahashi, Y. Matsuzawa, S. Tanaka, R.G. Nelson, W.C. Knowler, R.S. Lindsay, R.L. Hanson, J. Clin. Endocrinol. Metab. **89**, 4010–4017 (2004)
45. K. Kato, H. Osawa, M. Ochi, Y. Kusunoki, O. Ebisui, K. Ohno, J. Ohashi, I. Shimizu, Y. Fujii, M. Tanimoto, H. Makino, Clin. Endocrinol. (Oxf) **68**, 442–449 (2008)
46. M. Matsuda, F. Kawasaki, H. Inoue, Y. Kanda, K. Yamada, Y. Harada, M. Saito, M. Eto, M. Matsuki, K. Kaku, Diabetes Res. Clin. Pract. **66**, S121–S123 (2004)
47. J. Koshimura, H. Fujita, T. Narita, T. Shimotomai, M. Hosoba, N. Yoshioka, M. Kakei, H. Fujishima, S. Ito, Biochem. Biophys. Res. Commun. **316**, 165–169 (2004)
48. T. Isobe, S. Saitoh, S. Takagi, H. Takeuchi, Y. Chiba, N. Katoh, K. Shimamoto, Eur. J. Endocrinol. **153**(1), 91–98 (2005). Jul
49. A.M. Kanaya, C. Wassel Fyr, E. Vittinghoff, P.J. Havel, M. Cesari, B. Nicklas, T. Harris, A.B. Newman, S. Satterfield, S.R. Cummings, Health ABC Study, J. Clin. Endocrinol. Metab. **91**(12), 5044–5050 (2006). Dec
50. Y. Zhang, R. Proenca, M. Maffei, M. Barone, L. Leopold, J.M. Friedman, Nature **372**, 425–432 (1994)
51. J.M. Friedman, J.L. Halaas, Nature **395**, 763–770 (1998)
52. I.S. Farooqi, T. Wangensteen, S. Collins, W. Kimber, G. Matarese, J.M. Keogh, E. Lank, B. Bottomley, J. Lopez-Fernandez, I. Ferraz-Amaro, M.T. Dattani, O. Ercan, A.G. Myhre, L. Retterstol, R. Stanhope, J.A. Edge, S. McKenzie, N. Lessan, M. Ghodsi, V. De Rosa, F. Perna, S. Fontana, I. Barroso, D.E. Undlien, S. O'Rahilly, N. Engl. J. Med. **356**, 237–247 (2007)
53. C.T. Montague, I.S. Farooqi, J.P. Whitehead, M.A. Soos, H. Rau, N.J. Wareham, C.P. Sewter, J.E. Digby, S.N. Mohammed, J.A. Hurst, C.H. Cheetham, A.R. Earley, A.H. Barnett, J.B. Prins, S. O'Rahilly, Nature **387**, 903–908 (1997)
54. M. Maffei, J. Halaas, E. Ravussin, R.E. Pratley, G.H. Lee, Y. Zhang, H. Fey, S. Kim, R. Lallone, S. Ranganathan, P.A. Kern, J.M. Friedman, Nat. Med. **1**, 1155–1161 (1995)
55. S.G. Wannamethee, J. Tchernova, P. Whincup, G.D. Lowe, A. Kelly, A. Rumley, A.M. Wallace, N. Sattar, Atherosclerosis **191**, 418–426 (2007)
56. K.R. Segal, M. Landt, S. Klein, Diabetes **45**, 988–991 (1996)
57. A.E. Kitabchi, G.E. Umpierrez, J. Clin. Endocrinol. Metab. **88**, 2593–2596 (2003)
58. S. Dagogo-Jack, Diabetes Rev. **7**, 23–28 (1999)
59. G.R. Hajer, T.W. van Haeften, F.L. Visseren, Eur. Heart J. **29**, 2959–2971 (2008)
60. R.E. Ostlund Jr., J.W. Wang, S. Klein, R. Gingerich, Relation between plasma leptin concentration and body fat, gender, diet, age, and metabolic covariates. J. Clin. Endocrinol. Metab. **81**, 3909–3913 (1996)
61. M.I. Schmid, B.B. Duncan, A. Vigo, J.S. Pankow, D. Couper, C.M. Ballantyne, R.C. Hoogeveen, G. Heiss, Diabetologia **49**, 2086–2096 (2006)
62. A.M. Kanaya, F.C. Wassel, E. Vittinghoff, T.B. Harris, S.W. Park, B.H. Goodpaster, F. Tylavsky, S.R. Cummings, Arch. Intern. Med. **166**, 350–356 (2006)
63. H. Hama, A. Saito, T. Takeda, A. Tanuma, Y. Xie, K. Sato, J.J. Kazama, F. Gejyo, Endocrinology **145**, 3935–3940 (2004)
64. A. Saito, T. Takeda, H. Hama, Y. Oyama, K. Hosaka, A. Tanuma, R. Kaseda, M. Ueno, S. Nishi, S. Ogasawara, F. Gondaira, Y. Suzuki, F. Gejyo, Nephrology **10**, S26–S31 (2005)
65. B. Fruehwald-Schultes, W. Kern, J. Beyer, T. Forst, A. Pfutzner, A. Peters, Metabolism **48**, 1290–1293 (1999)
66. H. Asakawa, K. Tokunaga, F. Kawakami, J. Diabetes Complicat. **2**, 57–62 (2001)
67. G. Uckaya, M. Ozata, Z. Bayraktar, V. Erten, N. Bingol, I.C. Ozdemir, Diabetes Care **23**, 371–376 (2000)
68. C.E.M. De Block, I.H. De Leeuw, L.F. Van Gaal, Diabetes Care **28**, 1649–1655 (2005)
69. M. Matsuda, F. Kawasaki, H. Inoue, Y. Kanda, K. Yamada, Y. Harada, M. Saito, M. Eto, M. Matsuki, K. Kaku, Diabetes Res. Clin. Pract. **66**, S121–S123 (2004)
70. A. Gottsater, B. Ahren, G. Sundkvist, Diabetes Care **22**, 1913–1914 (1999)
71. J. Doupis, T.E. Lyons, S. Wu, C. Gnardellis, T. Dinh, A. Veves, J. Clin. Endocrinol. Metab. **94**, 2157–2163 (2009)
72. D.G. Haider, K. Schindler, G. Schaller, G. Prager, M. Wolzt, B. Ludvik, J. Clin. Endocrinol. Metab. **91**, 1578–1581 (2006)
73. M.P. Chen, F.M. Chung, D.M. Chang, J.C. Tsai, H.F. Huang, S.J. Shin, Y.J. Lee, J. Clin. Endocrinol. Metab. **91**, 195–299 (2006)
74. J. Zhu, M. Schott, R. Liu, C. Liu, B. Shen, Q. Wang, X. Mao, K. Xu, X. Wu, S. Schinner, C. Papewalis, W.A. Scherbaum, C. Liu, Horm. Metab. Res. **40**, 801–805 (2008)
75. D.G. Haider, G. Schaller, S. Kapiotis, C. Maier, A. Luger, M. Woltz, Diabetologia **49**, 1909–1914 (2006)
76. T. Dogru, A. Sonmez, I. Tasci, E. Bozoglu, M.I. Yilmaz, H. Genc, G. Erdem, M. Gok, N. Bingol, S. Kilic, T. Ozgurtas, S. Bingol, Diabetes Res. Clin. Pract. **76**, 24–29 (2007)
77. R. Retnakaran, B.S. Youn, Y. Liu, A.J. Hanley, N.S. Lee, J.W. Park, E.S. Song, V. Vu, W. Kim, R. Tungtrongchitr, P.J. Havel, M.M. Swarbrick, C. Shaw, G. Sweeney, Clin. Endocrinol. (Oxf) **69**, 885–893 (2008)
78. C.C. Lin, M.M. Lai, T.C. Li, C.I. Li, C.S. Liu, C.C. Chen, M.T. Wu, Diabetes Res. Clin. Pract. **85**, 24–29 (2009)
79. J. Berndt, N. Kloting, S. Kralisch, P. Kovacs, M. Fasshauer, M.R. Schon, M. Stumwoll, M. Bluher, Diabetes **54**, 2911–2916 (2005)

80. C. Pagano, C. Pilon, M. Olivieri, P. Mason, R. Fabris, R. Serra, G. Milan, M. Rossato, G. Federspil, R. Vettor, J. Clin. Endocrinol. Metab. **91**, 3165–3170 (2006)
81. Y.Y. Zhang, L. Gottardo, L. Thompson, C. Powers, D. Nolan, J. Duffy, M.C. Marescotti, A. Avogaro, A. Doria, Obesity **14**, 2119–2126 (2006)
82. Y. Bottcher, D. Teupser, B. Enigk, J. Berndt, N. Kloting, M.R. Schon, J. Thiery, M. Bluher, M. Stumvoll, P. Kovacs, J. Clin. Endocrinol. Metab. **91**, 2725–2731 (2006)
83. A. Körner, A. Garten, M. Blüher, R. Tauscher, J. Kratzsch, W. Kiess, J. Clin. Endocrinol. Metab. **92**(12), 4783–4791 (2007). Dec
84. H.K. Song, M.H. Lee, B.K. Kim, Y.G. Park, G.J. Ko, Y.S. Kang, J.Y. Han, S.Y. Han, K.H. Han, H.K. Kim, D.R. Cha, Am. J. Physiol. Renal Physiol. **295**(5), F1485–F1494 (2008)
85. M.I. Yilmaz, M. Saglam, A.R. Qureshi, J.J. Carrero, K. Caglar, T. Eyileten, A. Sonmez, E. Cakir, Y. Oguz, A. Vural, M. Yenicesu, P. Stenvinkel, B. Lindholm, J. Axelsson, Nephrol. Dial. Transplant. **23**, 1621–1627 (2008)
86. K. Hida, J. Wada, J. Eguchi, H. Zhang, M. Baba, A. Seida, I. Hashimoto, T. Okada, A. Yasuhara, A. Nakatsuka, K. Shikata, S. Hourai, J. Futami, E. Watanabe, Y. Matsuki, R. Hiramatsu, S. Akagi, H. Makino, Y.S. Kanwar, Proc. Natl Acad. Sci. USA **102**, 10610–10615 (2005)
87. J. Wada, Exp. Opin. Invest. Drugs **17**, 327–333 (2008)
88. N. Klöting, J. Berndt, S. Kralisch, P. Kovacs, M. Fasshauer, M.R. Schon, M. Stumvoll, M. Blüher, Biochem. Biophys. Res. Commun. **339**, 430–436 (2006)
89. J. Seeger, M. Ziegelmeier, A. Bachman, U. Lössner, J. Kratzch, M. Blüher, M. Stumvoll, M. Fasshauer, J. Clin. Endocrinol. Metab. **93**, 247–251 (2008)
90. B.S. Youn, N. Klöting, J. Kratzsch, N. Lee, J.W. Park, E.S. Song, K. Ruschke, A. Oberbach, M. Fasshauer, M. Stumvoll, M. Blüher, Diabetes **57**, 372–377 (2008)
91. Q. Li, R. Chen, J. Moriya, J. Yamakawa, H. Sumino, T. Kanda, T. Takahashi, J. Intern. Med. Res. **36**, 625–629 (2008)
92. K. Kempf, B. Rose, T. Illig, W. Rathmann, K. Strassburger, B. Thorand, C. Meisinger, H.E. Wichmann, C. Herder, C. Vollmert, Exp. Clin. Endocrinol. Diabetes. Aug 25 (2008). doi:10.1055/s-2008-1081499
93. N.E. Gulcelik, J. Karakaya, A. Gedik, A. Usman, A. Gurlek, Eur. J. Endocrinol. **160**, 65–70 (2009)
94. B.K. Tan, D. Heutling, J. Chen, S. Farhatullah, R. Adya, S.D. Keay, C.R. Kennedy, H. Lehnert, H.S. Randeva, Diabetes **57**, 1501–1507 (2008)