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Editorial

Vascular dysfunction: a Janus face of visfatin in diabetes?

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The escalating global diabetic population is estimated to reach a total of 366 million by 2030 [1]. Accordingly, type 2 diabetes mellitus (T2DM), the most common form of diabetes that stems from peripheral insulin resistance or dysfunctional pancreatic beta-cell function, is also approaching pandemic proportions. These alarming health changes are primarily fueled by the prevalence of obesity arising in part from increasingly sedentary lifestyles and high-fat diets [1]. Although surfeit weight is notably deleterious, obesity appears to be heterogeneous because not every overweight subject presents with the same cardiometabolic risk profile. In fact, epidemiologic studies suggest that visceral (omental) adipose tissue is more pernicious than subcutaneous (gluteal) adipose tissue, subjecting "apple-shaped" individuals to higher diabetes and cardiovascular risks than their "pear-shaped" counterparts [2].

Both visceral and subcutaneous adipose tissue synthesize and secrete a repertoire of cytokine-like peptides termed adipokines that can modulate insulin sensitivity and glucose metabolism [3]. Using a differential display method, Fukuhara and colleagues [4] recently identified visfatin as a putative adipokine that is predominantly produced in visceral fat. Visfatin, otherwise termed pre–B-cell colony-enhancing factor, was originally isolated from a human peripheral blood lymphocyte complementary DNA library and found to be also expressed in human bone marrow, liver tissue, and muscle [5]. The Fukuhara et al study was the first to positively correlate sera visfatin levels with visceral but not subcutaneous fat composition in both mice and humans [4]. Other investigators have since demonstrated that the visfatin gene is expressed in adipocytes [6] and that it is subjected to regulation [7] thereby quashing implications that visfatin may not be a true adipokine [8]. Visfatin expression increases concomitantly with differentiation of 3T3-L1 adipocytes in vitro and correspondingly rises at the spontaneous onset of obesity in KKA^y mice [4], supporting the notion that visfatin is fundamental to the pathophysiology of obesity. Paradoxically, short-term recombinant visfatin supplements trigger hypoglycemic responses in 2 diabetic mouse models, whereas adenovirus-mediated visfatin overexpression in KKA^y mice diminishes plasma levels of both glucose and insulin [4]. In accord, visfatin$^{+/-}$ mice have higher plasma glucose levels than their wild-type counterparts independent of satiety status [4]. Visfatin also prompts insulinlike glucose mobilization in adipocytes, myocytes, and hepatocytes in vitro and activates the insulin signaling transduction pathways in vivo, some or all of which possibly arise from the interaction between visfatin and the insulin receptor [4]. The binding affinity (K_D) of visfatin for the insulin receptor is similar to that of insulin itself (~5 nmol/L), and both peptides display comparable pharmacokinetic profiles in mice [4]. Is visfatin therefore a proponent of obesity with antidiabetogenic properties?

Takebayashi and colleagues [9] describe in this issue 2 studies investigating the potential link between visfatin and T2DM in Japanese subjects. The first cross-sectional study cohort was composed of 80 patients with T2DM and 28 age-matched healthy control individuals. The second prospective study cohort involved 20 subjects with T2DM on a 12-week pioglitazone regimen and 7 unmatched patients with T2DM after insulin therapy. Single measurements of plasma visfatin levels in the cross-sectional study were independent of health status, sex, and ongoing therapeutic measures. However, the investigators determined that $\log_{10}$ plasma visfatin values were negatively associated with flow-mediated dilation, creatinine clearance, and $\log_{10}$ plasma aldosterone. Long-term pioglitazone therapy in the second cohort elevated plasma visfatin (women only) and high-density lipoprotein levels while decreasing fasting plasma glucose (women only) and glycosylated hemoglobin (HbA_{1c}) levels, insulin resistance, and triglyceride concentrations.

The finding that circulating visfatin levels were indistinguishable between T2DM and normoglycemic persons in the Takebayashi et al report [9] contrasts with recent reports

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showing higher plasma visfatin levels in patients with T2DM [6,10,11]. Although these discrepancies could have resulted from differences in baseline characteristics or may have been negated had they been reported against waist-hip ratios [10], it is equally likely that they were the consequence of the relatively small cohort sizes monitored [6,9-11] coupled with the different drug interventions in place that may themselves modulate plasma visfatin levels [11]. Indeed, the difference in renal function between subjects as reported by Takebayashi and colleagues may also account for some of the differences. More striking is that the circulating levels of visfatin measured by Takebayashi's group were between 1.525 and 2.9 ng/mL [9]. Although Haider and colleagues [12] have reported similarly low plasma levels of visfatin, most investigators have found adult human circulating visfatin concentrations to be in the range of 14 and 50 ng/mL [4,6,10,11,13]. Because there is currently only one ELISA kit available for quantifying visfatin levels, one would expect that reproducibility issues would be of minimal concern. The large window of visfatin values reported is somewhat disconcerting and beckons the consideration of possible circadian influences [14] as well as the need to perform multiple (as opposed to singletons) assessments of plasma visfatin levels in every subject. More standardized methods of sample collection and storage may also be vital to limit the variability in visfatin quantification observed to date.

Endothelial dysfunction commonly presents in individuals with T2DM [15]. However, controversy persists as to whether this phenomenon primarily arises from direct vascular defects or if it is secondary to the presence of visceral obesity and a deranged metabolic milieu that are characteristic of many patients with T2DM [16]. Results from the cross-sectional Takebayashi cohort [9] allude to an inverse correlation between plasma visfatin levels and flow-mediated dilation in T2DM subjects. This relationship was strongly evident when data from all the patients with T2DM were included in the analysis and persisted, albeit less so upon removal of data from 2 individuals who had outlying (higher) circulating visfatin levels. Although preliminary, these initial observations concur with earlier clinical data suggesting a positive relationship between circulating visfatin and the manifestation of T2DM. As to whether this association is causal or visfatin is just a biomarker remains to be determined. Nonetheless, the novelty of the Takebayashi et al work lies in the description of a potential vascular role for visfatin, as earlier investigations have focused predominantly on its metabolic effects. Endothelial dysfunction is the product of impaired endothelium-dependent vasodilation and ultimate vasoconstrictor dominance. Often, this is the result of reduced nitric oxide and/or prostacyclin bioavailability as well as enhanced events along the endothelin-1 axis. Inasmuch as many adipokines exert multifaceted effects on vasoregulators [3], it would not be unreasonable to infer that visfatin may also critically alter the expression and/or activities of nitric oxide, prostacyclin, and endothelin-1. Interestingly, the authors were unable to establish any definite association between plasma visfatin levels and circulating concentrations of adiponectin, C-reactive protein, and fibrinogen, all of which modulate inflammation and endothelial function and have been implicated in the pathogenesis of diabetes [3].

The thiazolidinediones (TZDs) are peroxisome proliferator–activated receptor γ (PPARγ) agonists that are widely prescribed to patients with T2DM to improve insulin resistance and glucose control. Inasmuch as PPARγ is primarily expressed in adipose tissue, the insulin-sensitizing effects of TZDs are likely dependent on adipose tissue. Two-week pioglitazone treatment elevated visfatin messenger RNA levels in the adipose tissue of KKA^y mice [14], but neither 3- nor 4-week pioglitazone regimens altered adipose visfatin gene expression or circulating visfatin levels in T2DM and nondiabetic subjects [6]. Takebayashi and colleagues [9] report that pioglitazone correspondingly raised plasma visfatin levels and lowered fasting glucose concentrations in female subjects with T2DM after 12 weeks of treatment, and combined data from the mixed-gender cohort indicated that this TZD also appreciably lowered HbA_{1c} and homeostasis model assessment of insulin resistance values. Although the beneficial metabolic changes were predictable, the gender distinction was unexpected and suggests a potential hormonal influence. Interestingly, insulin treatment that is administered to both sexes also evoked sex-specific, men-only changes in fasting plasma glucose and HbA_{1c} levels. This anomaly coupled with the small cohort size (27 patients) and the ongoing concerns with visfatin measurements thus cautions conclusive interpretation of the data at this time. Insulin resistance often corresponds with impaired endothelial function. The metabolic benefits of visfatin demonstrated in the second study group coupled with that in the first cohort showing a detrimental influence of visfatin on vascular function suggest that visfatin may have conflicting actions within the realm of T2DM.

The original Fukuhara study [4] triggered much excitement, as the data suggested that the insulinlike actions of visfatin could potentially be harnessed for therapeutic advancements. However, the findings that ensued along with those of Takebayashi et al [9] have been confounding. Notably, Berndt and colleagues [13] failed to detect any difference in visfatin gene expression between visceral and subcutaneous fat in humans and were also unable to find any correlations between visceral fat mass and plasma visfatin concentrations. Nevertheless, the identification of an endogenous insulin mimetic regardless of its potential Janus vascular actions provides the unique opportunity to delve into and further elucidate the mechanisms underlying the hypoglycemic effects of insulin. The jury, however, is still out on whether plasma visfatin levels have any vasculometabolic relevance in T2DM or if this novel adipokine is merely a red herring. Further prospective studies in larger anthropomorphically matched cohorts

coupled with more detailed animal- and cell-based experiments are now clearly warranted.

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