

# Diabetes Mellitus: Are adipocytes passive depot of energy or have any role in energy balance?

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Type 2 diabetes mellitus was once considered a rare disease, but recently there has been an explosive increase in its incidence. Insulin resistance and hyperinsulinemia are characteristics of both type 2 diabetes and impaired glucose tolerance. These metabolic derangements, combined with hypertension and dyslipidemia, common in type 2 diabetes and impaired glucose tolerance, markedly increase the risk of cardiovascular, peripheral vascular, and cerebrovascular disease.

About 16 million Americans have type 2 diabetes, and at least an equal number have impaired glucose tolerance.<sup>1</sup> In 1994 WHO estimated that over 100 million people have diabetes affecting on an average around 6% of adult population (adults are described as group of people between the ages of 30-64 years). In 1992 over 11,000 Pakistanis died due to diabetes.<sup>2</sup> Type 2 diabetes accounts for most of the current and forecasted figures. Underdeveloped countries are shouldering most of the burden and by 2025, approximately 2.7 million people in Pakistan may have the disease yet only 0.8 million have been diagnosed. Individuals with diabetes face not only a shortened life span but also probability of incurring acute and chronic complications. Diabetes tends to increase with age in Pakistan. The prevalence doubles comparing young rural and oldest rural women increasing from 5% for the 25-44 years of age to 12% in the 65 years or over age group. The highest prevalence is among urban females 45-64 years of age with nearly 20% rise.<sup>3</sup> In addition to these alarming absolute rises in numbers, there is also a worsening trend for the disease to affect younger age groups. In developed countries the sharpest increase affects the over 65 year age group, unlike the situation in developing countries, where most new cases occur in those between 44 and 65 years of age.

Why has the incidence of type 2 diabetes increased so rapidly? Considerable epidemiologic evidence points to excess caloric intake and physical inactivity as the major reasons. A chronic imbalance between energy expenditure and energy intake causes obesity, which is one of the most potent risk factors for insulin resistance and type 2 diabetes.

These epidemiologic observations underscore the importance of the relation of adipose tissue to insulin resistance and glucose intolerance. Recent studies have transformed our thinking about the adipocyte. It is no longer regarded as a passive depot for storing excess energy in the

form of triglyceride, but as a cell that actively regulates the pathways responsible for energy balance and whose activity is controlled by a complex network of hormonal and neuronal signals. Adipocytes produce and secrete a variety of biologically active molecules, conceptualized as adipocytokines, including tumor necrosis factor (TNF)  $\alpha$ , adiponectin, leptin, resistin, plasminogen activator inhibitor-1 and heparin-binding epidermal growth factor (EGF)-like growth factor (HB-EGF). Several lines of evidences suggest that dysregulated production of adipocytokines participates in the development of metabolic and vascular diseases related to obesity.<sup>4</sup> Whether triglycerides are stored in adipocytes or broken down and released from adipocytes depends on whether there is a positive or negative energy balance, respectively. The adipocyte actively modulates energy balance through the secretion of hormones and other signaling molecules. For example, leptin is secreted by triglyceride-laden adipocytes, travels through the circulation, crosses the blood-brain barrier, and reaches the hypothalamus, where it modulates a host of neuroendocrine and autonomic nervous system activities, resulting in decreased food intake and increased energy expenditure. Resistin, as well as tumor necrosis factor, adiponectin, free fatty acids, and possibly other factors released by adipocytes, act in peripheral tissues to influence sensitivity to insulin and other cellular and metabolic processes involved in the use and partitioning of substrates.

Resistin was identified by Steppan and co workers<sup>5</sup> in mice by screening for genes that were induced during the differentiation of adipocytes but were down-regulated in mature adipocytes exposed to Rosiglitazone, an insulin-sensitizing drug used routinely in type 2 diabetes. Mouse resistin contains 114 amino acids and circulates as a homodimer of two peptides joined by a disulfide bridge.<sup>6</sup> Resistin (FIZZ3) is a member of the newly discovered cysteine-rich secretory protein family referred to as RELM or FIZZ. FIZZ3 is produced in adipose tissue and was shown to antagonize insulin action.<sup>7</sup> Resistin concentrations are increased in diet-induced obesity as well as in genetic models of obesity and insulin resistance. Furthermore, resistin gene expression is markedly down-regulated by treatment with antidiabetic drugs called Thiazolidinediones, which improve target-tissue sensitivity to insulin. A possible role in inflammatory processes is suggested.

Adiponectin is an adipose-tissue-derived protein with important metabolic effects. Its production and/or secretion is increased by IGF-1 and by activators of PPAR $\alpha$ . Its concentrations are decreased by TNF- $\alpha$ , glucocorticoids,  $\beta$ -adrenergic agonists, and cAMP. In addition to inhibiting inflammatory pathways, recombinant adiponectin increases insulin sensitivity and improves glucose tolerance in animal models. Genetic variants in the adiponectin gene itself and/or in genes encoding adiponectin-regulatory proteins may be associated with hypoadiponectinemia, insulin resistance, and type 2 diabetes.

The adipocyte-derived hormone leptin regulates food intake and systemic fuel metabolism. Leptin receptors are produced most abundantly in the brain but are also present in several peripheral tissues. Studies on the role of leptin in controlling energy homeostasis have to date focused on brain receptors and neuroendocrine pathways that regulate feeding behavior and sympathetic nervous system activity. Leptin acts synergistically with fibroblast growth factor-2 and vascular endothelial growth factor to stimulate angiogenesis and can also influence vascular permeability. Leptin induced neovascularization in corneas from normal rats, but not in corneas from leptin receptor-deficient (*fa/fa*) rats, indicating that the vascular effects were mediated via the leptin receptor. Leptin administration also increased vascular lesion formation in injured arteries in leptin-deficient (*ob/ob*) mice, but this response was markedly attenuated in leptin receptor-deficient (*db/db*) mice, providing strong evidence for direct effects of leptin on the arterial wall.<sup>9</sup>

Ghrelin activates GHS-Rs located on the pituitary and GH-releasing hormone-containing neurons in the hypothalamic arcuate nucleus, stimulating GH release.<sup>6</sup> The activation of GHS-Rs by Ghrelin on NPY/agouti-related peptide (AGRP)-producing neurons located in the arcuate nucleus stimulates food intake.<sup>10</sup> Ghrelin increases fat tissue by decreasing fat oxidation. Stimulation of motility and gastric emptying induced by ghrelin may involve a local effect as well as central mechanisms.<sup>11</sup> Ghrelin is much more than simply a natural GH secretagogue however, it also acts on other central and peripheral receptors and exhibits other actions, including stimulation of lactotroph and corticotroph secretion; it also influences gastroenteropancreatic functions and has orexigenic, metabolic, cardiovascular, and antiproliferative effects. Studies established that ghrelin stimulates food intake in rodents as well as in humans and is strongly involved in the regulation of energy homeostasis. Although several other potent orexigenic peptides, including NPY, AGRP, and melanin-concentrating hormone, have previously been characterized in the brain, ghrelin is the first food-intake-stimulating signal originating from the stomach.<sup>12</sup> Several assays (competitive RIA and sandwich

ELISA) have been developed by many manufacturers to measure leptin, its receptor, ghrelin, adiponectin, and resistin. All assays have good performance regarding detection limits, linearity, and precision. Leptin, its receptor, adiponectin, and resistin are stable, in contrast to ghrelin, which is labile and measured under difficult conditions. The concentrations of all of these hormones depend of the BMI.

It has been postulated that Type 2 diabetes mellitus is a manifestation of inflammatory host response. This host response is responsible orchestrated by production of pro and anti-inflammatory cytokines that are under genetic control of interleukin 6 and tumor necrosis factor, low production capacity for interleukin 10, a centrally operating cytokine with strong anti-inflammatory properties is associated with the metabolic syndrome. Interleukin 8 is potent chemoattractant and induces recruitment of neutrophils and T lymphocytes in the subendothelial space and adhesion of monocytes to the endothelium. Interleukin 18 (IL18) is potent pro-inflammatory cytokine that is reported to play a role in plaque destabilization and to be of value in predicting cardiovascular death in patients with coronary artery disease.<sup>13</sup>

The newly discovered secretory function of the adipocytes has shifted the view of the white adipose tissue from a simple energy storage tissue to a major endocrine system, the hormones of which influence energy homeostasis, glucose and lipid metabolism, vascular homeostasis, immune response, and even reproduction and fibrotic diseases. As obesity, insulin resistance and diabetes mellitus are of major concern not only in developed countries but in developing countries like Pakistan, so it is the need of the hour to carry out research in our country also on the role of adipocytokines in energy metabolism which may emerge as early markers for diabetes or may turn out to be effective therapeutic agents for it.

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