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Bioinformatics Analysis of Some Functional Genes and Proteins Involved in Obesity-Induced Type 2 Diabetes

[1]Ehab M. Abdella, [1]Rasha R. Ahmed, [1]Mohamed B. Ashour, [1]Osama M. Ahmed, [2]Sameh F. Abu Zid and [1]Ayman M. Mahmoud

[1]Experimental Obesity and Diabetes Research Lab, Department of Zoology, Faculty of Science,
[2]Department Pharmacognosy, Faculty of Pharmacy,
Beni-Suef University, Beni-Suef, Egypt

ABSTRACT

The incidence of type-2 diabetes is rising rapidly worldwide, mainly because of the increase in the incidence of obesity, which is an important risk factor for this condition. Both obesity and type-2 diabetes are complex genetic traits but they also share some nongenetic risk factors. Differences among individuals in their susceptibility to both these conditions probably reflect their genetic constitutions. The dramatic improvements in genomic and bioinformatic resources are accelerating the pace of gene discovery. It is tempting to speculate the key susceptible genes/proteins that bridges diabetes mellitus and obesity. In this regard, we evaluated the role of several genes/proteins that are believed to be involved in the evolution of obesity associated diabetes through thorough literature search. Also we analyzed the data pertaining to genes of these proteins extracted from the databases that are available online for free access. The functional cDNA sequences of these genes/proteins are extracted from National Center for Biotechnology Information (NCBI) and Ensembl Genome Browser. Our bioinformatic analysis reports 21 genes as ominous link with obesity associated diabetes. Also this study indicated that, adipose tissue is now known to express and secrete a variety of metabolites, hormones and cytokines that have been implicated in the development of insulin resistance.This bioinformatic study will be useful for future studies towards therapeutic inventions of obesity associated type-2 diabetes.

Keywords: Bioinformatics, Functional Genes, Obesity and Type Two Diabetes

1. INTRODUCTION

Type 2 diabetes and its complications may be prevented by either avoiding factors that trigger the disease process (primary prevention) or using therapies that modulate the disease process before the onset of clinical symptoms (secondary prevention). Accurate prediction and identification using biomarkers will be useful for disease prevention and initiation of proactive therapies to those individuals who are most likely to develop the disease. Recent technological advances in genetics, genomics, proteomics and bioinformatics offer great opportunities for biomarker discovery (Gedela *et al*., 2007).

Obesity and its pathological complications, including atherosclerosis, hypertension and insulin resistance, have increased to reach epidemic dimensions nowadays (Bray, 2004). Some important factors for the development of these disorders are excessive accumulation of abdominal fat, which is known to play an important role in development of chronic inflammation; deposition of lipids into non-adipose tissues such as liver and muscles; atherosclerosis and chronic inflammation that increase risk in cardiovascular disorders and diabetes (Rajala and Scherer, 2003).

Adipose tissue is not just a site of energy storage but also behaves as a dynamic endocrine organ (Kershaw and Flier, 2004). It also plays an important role in energy expenditure, both as depot for energy-rich triglycerides and

Corresponding Author: Osama M. Ahmed, Division of Physiology, Department of Zoology, Faculty of Science, Beni-Suef University, Salah Salem Street, PO: 62514, Beni-Suef, Egypt Tel: 002 01064006605

as a source for metabolic hormones as well (Bastard *et al*., 2006; Desruisseaux *et al*., 2007). Adipocytes produce a large number of so-called adipokines, such as leptin, adiponectin, Interleukin (IL)-1β, IL-6 and Tumor Necrosis Factor-alpha (TNF-α). Some of these molecules affect energy metabolism and insulin sensitivity in other tissues such as muscle and liver (Guilherme *et al*., 2008). During obesity, lipid storage in adipocytes is increased, which triggers the release of adipokines (Hotamisligil, 2006; Lupinacci *et al*., 2009). During inflammation, the mature adipocytes of the adipose tissue are responsible for increasing production of pro-inflammatory adipokines (Simons *et al*., 2005), including mentioned TNF-α, IL-1β, IL-6. That disregulation contributes to obesity and chronic inflammation (Ouchi *et al*., 2003). The local increase of these adipokines have been directly related to insulin resistance, increasing lypolisis and increasing leptin levels (Desruisseaux *et al*., 2007).

The growing incidence of type 2 diabetes with increasing obesity reflects that obesity is an emerging risk factor for the progression of insulin resistance and subsequently to overt type-2 diabetes. Both in normoglycemic and hyperglycemic states, obese people exhibit a higher degree of hyperinsulinemia that correlates with the degree of insulin resistance, in order to maintain normal glucose tolerance (Bonadonna *et al*., 1990). Following attainment of certain point, the progressive deterioration of the metabolic milieu leads to eventual failure of hyperinsulinemia to compensate fully for the insulin resistance and thereby produces impaired glucose tolerance that progress to overt diabetes (DeFronzo *et al*., 1992). It has been presumed from genetic studies that there could be subset of genes whose expression changes with obesity and those genes whose expression further changes in the progression to type-2 diabetes (Elbers *et al*., 2007; Wang and Eckel, 2009; Ocana *et al*., 2010). However, the molecular basis that links obesity and diabetes is still largely unknown.

Bioinformatics has been in the focus since recent years for unraveling the structure and function of complex biological mechanisms. The analysis of primary gene products has further been considered as diagnostic and screening tool for disease recognition. Such strategies aim at investigating all gene products simultaneously in order to get a better overview about disease mechanisms and to find suitable therapeutic targets. Recently Gerken *et al*. (2007) performed bioinformatics analysis and reported that the variants in the fat mass and obesity associated gene are associated with increased body mass index in humans. Although Elbers *et al*. (2007) identified five overlapping chromosomal regions for obesity and diabetes. These results illustrate the importance of proteomics and bioinformatics approaches for identify new therapeutic invention of obesity is a challenging subject.

This study will therefore focus on potential implications of bioinformatics as a tool to identify novel metabolic patterns or markers associated with disease status. We will exemplify the potential of this method using the association between specific fats and development of obesity associated diabetes as a test case. In the present study we have employed online bioinformatics tools for the analysis of 21 genes, which are expected to play major role in obesity and diabetes, we sought to identify the common central gene/protein that connects both the metabolic disorders such as obesity and diabetes.

2. MATERIALS AND METHODS

2.1. Methodology

The present research aims at finding the genes/proteins responsible for obesity associated diabetes in two phases. The first phase of the research attempts to identify the candidate genes/proteins which are involved in these disorders through thorough literature search. The second phase of the research analyzes the data pertaining to genes of these proteins obtained from the databases that are available online for free access. The functional cDNA sequences of these genes/proteins are extracted from: (1) National Center for Biotechnology Information (NCBI), (http\\www. ncbi.nih.nlm.gov), (2) Rat Genome Database (RGD) (<http://rgd.mcw.edu/rgdweb /search/search.html>), (3) Online Mendelian Inheritance in Man (OMIM), which can be accessed with the Entrez database searcher of the National Library of Medicine, Ensembl Genome Browser (http\\www.ensembl.org/index.html), (4) Mouse Genome Informatics (MGI) website is hosted by The Jackson Laboratory, (5) HomoloGene, a tool of the National Center for Biotechnology Information (NCBI), is a system for automated detection of homologs (similarity attributable to descent from a common ancestor) among the annotated genes of several completely sequenced eukaryotic genomes and (6) GeneCards is a database of human genes that provides genomic, proteomic, transcriptomic, genetic and functional information on all known and predicted human genes. GeneCards is being developed and maintained by the Crown Human Genome Center at the Weizmann Institute of Science.

3. RESULTS

3.1. First Phase (Literature Search)

From literature search several adipocyte-secreted factors has been demonstrated to potentially link obesity, insulin resistance and type 2 diabetes mellitus.

Table 1. Showing thorough literature search of the genes/proteins that have been studied in the present study, which are believed to be involved in type-2 diabetics and obesity

Gene name	Biological processes
Adiponectin	It enhances insulin resistance through activation of AMP protein kinase (AMPK). In addition, it also affects hepatic glucose production by decreasing the mRNA expression of two essential gluconeogenic enzymes, phosphoenol pyruvate, carboxykinase and glucose-6-phosphate (Kadowaki and Yamauchi, 2005; Antunna-Puente *et al*., 2008).
Resistin (RETN)	It links obesity to type-2 diabetes. Several studies showed that resistin expression was increased in obese animals and decreased in the presence of thiazolidinediones. A recent study revealed a decrease in fasting glucose, improved glucose tolerance and enhanced insulin sensitivity in resistin gene knockout mice (Antunna-Puente *et al*., 2008). Moreover, resistin inhibits adipocyte differentiation (Kim *et al*., 2001). In addition, the absence of resistin could allow activation of AMPK and reduce gene expression encoding for hepatic gluconeogenic enzymes. On the other hand, resistin has a role in inflammatory processes. It was associated with many inflammatory markers including C-reactive protein, TNF-a and IL-6. Thus, resistin may represent a link between inflammation and metabolic signals (Rabe *et al*., 2008).
Leptin (Obesity factor)	It is an adipocyte-derived hormone and cytokine that regulates energy balance through a wide range of functions, fatty acid metabolism and energy homeostasis. Several studies showed that, leptin play an important role in the central regulation of body weight. It is now apparent that leptin also has important functions as a metabolic and neuroendocrine hormone. Interestingly, plasma leptin levels correlate positively with body weight and it has been proposed that hyperleptinemia may be important in the development of insulin resistance associated with type 2 and gestational diabetes (Kahn and Flier, 2000).
TNF-a	It is a proinflammatory cytokine with a wide range of biologic effects including the stimulation of the production of prostaglandins, platelet-activating factor and plasminogen activator inhibitor; chemotaxis; the induction of adhesion molecules expression; the synthesis of other inflammatory mediators, inhibits lipolysis and impairs insulin-induced glucose uptake, thus leading to insulin resistance and weight loss (Antunna-Puente *et al*., 2008).
IL-6	Cytokines appear to be major regulators of adipose tissue metabolism. Expression studies show that adipocytes can synthesize Tumor Necrosis Factor Alpha (TNF-α) and several Interleukin (IL) notably IL-1β and IL-6. IL-1β is well known to suppress adipocyte differentiation and lipoprotein lipase expression and activity by inhibiting the expression of fatty acid transport protein in adipose tissue. In addition, It is an important regulator of adipogenesis, food intake and energy expenditure (Carey *et al*., 2008; Wang *et al*., 2010).
RBP-4	Recent studies indicated that RBP-4 serum level was elevated in insulin-resistant rodents and in obese or type 2 diabetic humans. In fact, there is a positive correlation between RBP-4 plasma levels and insulin resistance severity in obese, glucose intolerant, type 2 diabetics and in non-obese subjects with strong family background (Yang *et al*., 2005; Antunna-Puente *et al*., 2008).
Adipsin	It is a serine protease and part of alternative complement pathway (complement factor D). it is discovered as a factor expressed in a differentiation-dependent manner in adipocyte cell lines and its expression was greatly reduced in animal models of obesity. Thus this polypeptide may act as a lipostatic signal and may have a role linking insulin resistance with obesity (Trayhum and Beattie, 2001; Fruhbeck *et al*., 2004).
LPL	It plays a major role in the metabolism and transport of lipids. It is the enzyme responsible for the hydrolysis of core Triglycerides (TGs) in chylomicrons and very Low-Density Lipoproteins (VLDLs), producing chylomicron remnants and Intermediate-Density Lipoproteins (IDLs), respectively (Wang and Eckel, 2009). Besides its hydrolytic activity, LPL can interact with lipoproteins to anchor them to the vessel wall and facilitate lipoprotein particle uptake (Rinninger *et al*., 1998; Strauss *et al*., 2001; Long *et al*., 2006).
Ghrelin	It is a novel 28-amino-acid peptide esterified with octanoic acid on Ser 3 that is principally released from Gr cells in the oxyntic mucosa of the stomach (Chung *et al*., 2007). Ghrelin has been identified as an endogenous ligand for the GH Secretagogue Receptor (GHS-R) (Kojima *et al*., 1999). Ghrelin stimulates GH release via the hypothalamus and direct pituitary pathways and induces a positive energy balance by stimulating food intake while decreasing fat use through GH-independent mechanisms (Nakazato *et al*., 2001). Ghrelin also has numerous peripheral actions including direct effects on exocrine and endocrine pancreatic functions, carbohydrate metabolism, the cardiovascular system, gastric secretion, stomach motility and sleep (Kojima and Kangawa, 2005; Ghigo *et al*., 2005)
Chemerin	It is crucial for normal adipocyte differentiation and modulate the expression of adipocyte gene involved in glucose and lipid homeostasis by affecting glucose transporter-4, fatty acid synthase and adiponectin via its own receptors. In addition, it enhances insulin stimulated glucose uptake and Insulin Receptor Substrat-1 (IRS-1) tyrosin phosphorylation in 3T3-L1 adipocytes, suggesting that chemerin may increase insulin sensitivity in adipose tissue (Roh *et al*., 2007; Cash *et al*., 2008; Takahashi *et al*., 2008).
Visfatin	It was recently discovered as a new adipokines. Similarly to insulin, visfatin in vitro enhanced glucose uptake by monocytes and adipocytes and inhibited hepatocytes glucose release (Gualillo *et al*., 2007). In addition, visfatin amplifies adipocyte differentiation. Also, it has insulin mimetic effects can bind to and activate insulin receptors. This hormone also affects insulin-transduction pathway as it induces tyrosine phosphorylation of insulin receptor substrate-1 and -2 and activate phosphorylinositol-3-kinase B and MAP kinase (Antunna-Puente *et al*., 2008).
Omentin	Plasma omentin-1 levels were inversely correlated with obesity and insulin resistance and positively correlated with adiponectin and HDL-levels (De Souza *et al*., 2007; Rabe *et al*., 2008). Interestingly, omentin increases insulin-stimulated glucose uptake in both omental and subcutaneous adipocytes and promotes AKt phosphorylation (Yang *et al*., 2006; Antunna-Puente *et al*., 2008).

Table 1. Continue

PAI-1	PAI-1 inhibits the serine proteases tPA and uPA/urokinase and hence is an inhibitor of fibrinolysis, the physiological process that degrades blood clots. Also, PAI-1 inhibits the activity of matrix metalloproteinases, which play a crucial role in invasion of malignant cells across the basal lamina (Binder *et al*., 2002). In addition, it is implicated in adipose tissue development and in the control of insulin signaling in adipocytes. Also, it impairs insulin action. Thus, PAI-1 inhibitors may serve to improve insulin action (Hertig and Rondeau, 2004).
FABP2	The intracellular Fatty Acid-Binding Proteins (FABPs) belong to a multigene family with nearly twenty identified members. FABPs are divided into at least three distinct types, namely the hepatic-, intestinal- and cardiac-type. They form 14-15 kDa proteins and are thought to participate in the uptake, intracellular metabolism and/or transport of long-chain fatty acids. They may also be responsible in the modulation of cell growth and proliferation. Intestinal fatty acid-binding protein 2 gene contains four exons and is an abundant cytosolic protein in small intestine epithelial cells. This gene has a polymorphism at codon 54 that identified an alanine-encoding allele and a threonine-encoding allele. Thr-54 protein is associated with increased fat oxidation and insulin resistance (Glatz *et al*., 1997; Storch and Thumser, 2000).
PPAR-γ	The members of the PPAR-family, PPARα, PPARβ/δ and PPARγ play an important role in the regulation of lipid and glucose metabolism (Fliegner *et al*., 2008). Disturbance of PPAR pathways promotes the progression of diseases, such as obesity, type 2 diabetes, cardiovascular diseases, cancer, neurodegenerative diseases, hypertension and chronic inflammation (Michalik *et al*., 2006; Hamblin *et al*., 2009; Khateeb *et al*., 2010). Once activated by a ligand, PPARs recruit transcriptional co-activators, which are necessary to initiate target gene transcription. The target genes are mainly involved in the energy homeostasis and include genes from the ß-oxidation, the free fatty acid translocase (CD36), the Medium Chain Acetyl Dehydrogenase (MCAD), the Acetyl-CoA-Oxidase (ACO) and the carbohydrate oxidative pathways like the insulin-insensitive (GLUT1) and the insulin-sensitive (GLUT4) glucose transporters. These genes were first established as target genes of PPARα and β/δ, but recently it was shown that CD36, ACO and GLUT1 are also PPARγ target genes (Li *et al*., 2008). PPARγ is mainly involved in fat cell differentiation and lipid storage, but is also involved in the regulation of glucose homeostasis and cardiac energy metabolism (Hamblin *et al*., 2009). So that, PPAR-γ ligand could potentiate the insulin effect and improve insulin signaling via increasing tyrosine phosphorylation of the insulin receptors, as well as the serine phosphorylation of Akt/PKB (Wallberg *et al*., 2003). In addition, PPARs have been implicated as regulators of inflammatory processes and tissue repair. Thus, mechanisms of PPAR-induced pathways are under intensive investigation.
Aguti (AgRP)	It has been demonstrated to be an inverse agonist of melanocortin receptors, specifically, MC3-R and MC4-R. The melanocortin receptors, MC3-R and MC4-R, are directly linked to metabolism and body weight control. These receptors are activated by the peptide hormone α-MSH (melanocyte-stimulating hormone) and antagonized by the agouti-related protein (Backberg *et al*., 2004). The appetite stimulating effects of AgRP are inhibited by the hormone leptin and activated by the hormone ghrelin. Adipocytes secrete leptin in response to food intake. This hormone acts in the arcuate nucleus and inhibits the AgRP/NPY neuron from releasing orexigenic peptides (Enriori *et al*., 2007). Ghrelin has receptors on NPY/AgRP neurons that stimulate the secretion of NPY and AgRP to increase appetite. AgRP is stored in intracellular secretory granules and is secreted via a regulated pathway (Creemers *et al*., 2006). The transcriptional and secretory action of AgRP is regulated by inflammatory signals (Scarlett *et al*., 2008). Levels of AgRP are increased during periods of fasting. It has been found that AgRP stimulates the hypothalamic-pituitary-adrenocortical axis to release ACTH, cortisol and prolactin. It also enhances the ACTH response to IL-1-beta, suggesting it may play a role in the modulation of neuroendocrine response to inflammation (Xiao *et al*., 2003).
nSREBP-1	Shimomura *et al*. (1998) reported that, nuclear SREBP-1 was shown to promote adipocyte differentiation in cultured 3T3-L1preadipocytes. In addition, this protein have the ability to bind and activate the promoters of genes involved in cholesterol biosynthesis and uptake. The documented direct targets of nSREBP include 3-hydroxy-3-methyl glutaryl coenzyme A (HMG-CoA) synthase, HMG-CoA reductase (enzymes involved in cholesterol biosynthetic pathway), fatty acid synthase and glycerol 3-phosphate acyl-transferase. This nuclear protein also activate transcription of the low density lipoprotein receptors which mediates uptake of cholesterol and fatty acids (Brown and Goldstein, 1997).
FOXO1	It is a family of winged helix/forkhead box factors which are crucial for adipocyte differentiation and have prominent roles in insulin signaling pathways (Armoni *et al*., 2006). In addition, convergence of nuclear receptors and forkhead pathways in general and of FOXO1 and PPAR-γ in particular has been implicated in the pathophysiological states of insulin resistance and diabetes. Several studies showed that, FOXO1 also functions in adipose tissue to couple insulin signaling to adipogenesis, which involves switching pre-adipocytes from proliferation to terminal differentiation. Also, FOXO1 directly or indirectly represses expression of PPAR-γ gene which represses GLUT4 promoter activity. Based on this evidence, the repression of PPAR-γ by FOXO1 leads to GLUT4 up-regulation and results in enhanced glucose transport and cellular insulin sensitivity (Nakae *et al*., 2002; 2003; Tran *et al*., 2003).
11β-HSD-1	Data from rodents provide evidence for a casual role of 11β-HSD-1 in the development of obesity and its complications (Masuzaki *et al*., 2001; Boullu-Ciocca *et al*., 2005). Recent studies indicated that, 11β-HSD-1 expression was increased in visceral adipose tissue in obese patients. However, 11β-HSD-1 inhibition had therapeutic effect in murine models of metabolic syndrome or type 2 diabetes (Hermanowski-Vosatka *et al*., 2005; Desbriere *et al*., 2006).
Apelin	Apelin is active peptide regulate insulin resistance by influencing the circulating adiponectin level and the expression of brown adipose tissue uncoupling proteins and energy expenditure in mice (Gualillo *et al*., 2007; Higuchi *et al*., 2007).
Vaspin	Vaspin, a visceral adipose tissue-derived serine protease inhibitor, is strongly expressed in visceral adipose tissue in rat, mouse and human obesity (Hida *et al*., 2005). However, human mRNA was also expressed in subcutaneous adipose tissue (Rabe *et al*., 2008). Administration of recombinant human vaspin to a mouse model of diet-induced obesity improved glucose tolerance and insulin sensitivity, suggesting that vaspin may represent an insulin sensitizing adipokines (Antunna-Puente *et al*., 2008; Rabe *et al*., 2008).

Table 2. Showing comparative gene map data of the genes/proteins that have been studied in the present study, which are believed to be involved in type-2 diabetics and obesity

	Rattus norvegicus				Mus musculus				Homo sapiens			
Gene	Map name	Map position	Chr. number	Chr. position	Map name	Map position	Chr. number	Chr. position	Map name	Map position	Chr. number	Chr. position
Adiponectin	genome assembly 3.1	79965888	11	q23	Mouse genome assembly 36.1	23146609	16	16 B3–B4	human genome assembly	188043164	3	q27
Resistin	Rat Celera Assembly	3566836	12	p12	Mouse Celera Assembly	3886118	8	8 A1	Human Celera Assembly	7605160	19	p13.2
Leptin	Rat Celera Assembly	52779315	4	q22	Mouse Celera Assembly	29063769	6	6 A3.3	Human Celera Assembly	122684619	7	q31.3
TNF-α	genome assembly 3.1	64647455	10	q25	Mouse Genome Assembly 36.1	78336352	11	11 B5	human genome assembly	23686912	17	q22-q23
IL-6	genome assembly 3.1	456798	4	q11	Mouse genome assembly 36.1	30339701	5	5 B1	Human Celera Assembly	22752396	7	
RBP-4	Rat Celera Assembly	2.33E+08	1	q53	Mouse Celera Assembly	38908311	19	19 D1	human genome assembly	95341583	10	q23-q24
Adipsin	genome assembly 3.1	11325546	7	q11	Mouse Celera Assembly	80905663	10	10 C1	Human Celera Assembly	784591	19	p13.3
LPL	genome assembly 3.1	22532512	16	p14	Mouse Celera Assembly	71423790	8	8 B3.3	human genome assembly	19841057	8	p22
Ghrelin	genome assembly 3.1	1.5E+08	4	q42	Mouse genome assembly 36.1	113666113	6	6 E3	human genome assembly	10302433	3	p26-p25
Chemerin	Rat Celera Assembly	72460060	4	q24	Mouse Celera Assembly	49080699	6	6 B2.3	Human Celera Assembly	144592497	7	
Visfatin	genome assembly 3.1	51132285	6	q16	Mouse genome assembly 36.1	33505340	12	12 B1	human genome assembly	105495899	7	q22.3
Omentin	Genome Assembly 3.4	87445119	13	q24	Mouse genome assembly 36.1	173448254	1	1 H2	human genome assembly	157659404	1	q21.3
PAI-1	Rat Celera Assembly	21377028	12	q11-q12	Mouse Celera Assembly	134078340	5	5 G2	Human Celera Assembly	95778744	7	q21.3-q22
FABP2	genome assembly 3.1	219554563	2	q42	Mouse Genome Assembly 36.1	122598310	3	3 G1	human genome assembly	120596008	4	q28-q31
PPARγ	Rat Celera Assembly	137316681	4	q42	Mouse Celera Assembly	117199637	6	6 F3-F1	Human Celera Assembly	12266744	3	p25
Aguti (AgRP)	genome assembly 3.1	35391672	19	q11	Mouse Genome Assembly 36.1	108090598	8	8 D1-D2	human genome assembly	66073974	16	q22
nSREBF-1	Rat Celera Assembly	44264875	10	q22	Mouse Genome Assembly 36.1	60012591	11	11 B2	human genome assembly	17656110	17	p11.2
FOXO1	Rat Celera Assembly	130806706	2	q26	Mouse Celera Assembly	52001471	3	3 C	Human Celera Assembly	22187272	13	q14.1
11β-HSD1	genome assembly 3.1	109252609	13	q27	Mouse Genome Assembly 36.1	195047834	1	1 H6	human genome assembly	206266585	1	q32-q41
Apelin	genome assembly 3.1	134460719	X	q35	Mouse Genome Assembly 36.1	45378323	X	X A3.2	Human Celera Assembly	129165798	X	q25
Vaspin (Serpina12)	Rat Celera Assembly	120432630	6	q32	Mouse Genome Assembly 36.1	105266979	12	12 F1	human genome assembly	94023372	14	q32.13

These adipocytokines comprise mediators (**Table 1**) such as adiponectin, resistin, leptin (obesity factor), Tumor Necrosis Factor-Alpha (TNF-α), Interleukin-6 (IL-6), Retinol Binding Protein-4 (RBP-4), adipsin, Lipoprotein Lipase (LPL), ghrelin, chemerin, visfatin, omentin, Plasminogen Activator Inhibitor-1 (PAI-1), Fatty Acid Binding Protein-2 (FABP2), Peroxisome Proliferators-Activated Receptor-γ (PPARγ), Aguti (AgRP), nuclear Sterol Regulatory Element-Binding Proteins-1c (nSREBP-1), winged-helix-forkhead box class O-1 (FOXO-1), 11β-Hydroxysteroid Dehydrogenase type-1 (11β-HSD-1), apelin and vaspin. These adipose derived factors are presently subjected to intensive research concerning their involvement in the regulation of adipose tissue physiology and in particular, their potential implication in insulin resistance, obesity and diabetes. In addition, most of these mediators may directly or indirectly interact with insulin receptors and/or insulin signaling, leading to insulin resistance in liver and peripheral tissues, especially in visceral obesity. The roles and mechanisms of some of the most important adipokines were suggested by some publications illustrated in **Table 1**.

Table 3. Showing gene ontology data of the genes/proteins that have been studied in the present study, which are believed to be involved in type-2 diabetics and obesity

		Identifiers				gene ontology	
Gene	Secreted tissues	MGD	OMIM	Homolo-gene	Array IDs	Molecular function	Biological activities
Adiponectin	Adipose tissues	106675	605441	3525	rc_AI176736_at	hormone activity	- Positive regulation of I-kappaB kinase/NF-kappaB cascade - Negative regulation of gluconeogenesis - Positive regulation of fatty acid metabolic process - Positive regulation of glucose import
Resistin	Brain, cerebral cortex, lung	1888506	605565	10703	rc_AA819348_at	hormone activity	- Increase transcriptional events leading to an increased expression of several pro-inflammatory cytokines - Serve as a link between obesity and T2DM
Leptin	Adipocytes	104663	164160	193	D49653_s_at	growth factor activity	- Regulation of gluconeogenesis - Regulation of insulin secretion - Regulation of intestinal cholesterol absorption - Negative regulation of appetite
TNF-a	Numerous cells, but mainly macrophages and lymphocytes	104798	191160	496	rc_AA943494_at	Cytokine activity	- Induction of apoptosis via death domain receptors - Regulation of cell proliferation - Positive regulation of I-kappaB kinase/NF-kappaB cascade - Negative regulation of glucose import
IL-6	fibroblasts, lymphocytes, adipose tissues	96559	147620	502	M26745cds_s_at	Cytokine activity	- Cell-cell signaling - Positive regulation of cell proliferation - Negative regulation of apoptosis
RBP-4	Adipocyte tissue	97879	180250	4908	K03045cds_r_at	Transporter activity	Transport, visual perception and response to stimulus
Adipsin	White fat adipocytes		134350		GE1112269	Stimulates glucose transport in fat cells and inhibits lipolysis	- The encoded protein is a component of the alternative complement pathway best known for its role in humoral suppression of infectious agents and the encoded protein has a high level of expression in fat, suggesting a role for adipose tissue in immune system biology.
LPL	Adipose tissues	96820	238600	200	L03294_g_at	lipid transporter activity	- Regulate fatty acid metabolic process - Regulate lipid catabolic process
Ghrelin	produced by P/D1 cells lining the fundus of stomach	1930008	605353	9487	A_44_P420046	Hormone activity	- positive regulation of appetite - positive regulation of body size
Gene	Secreted tissues	MGD	OMIM	Homolo-gene	Array IDs	Molecular function	Biological Activities
Chemerin	Hepatocytes , white adipose tissue	1918910	601973	2167	rc_AI176061_at	cell differentiation activities	- Retinoid metabolic process
Visfatin	Visceral fat Adipocytes	1929865	608764	4201	rc_AI177755_at	cytokine activity	- cell-cell signaling, - positive regulation of cell proliferation
Omentin	visceral adipose tissue	3057189	609873	79454		Sugar binding activity	- Signal transduction
PAI-1	Endothelium cells lining blood vessels, adipose tissue	97608	173360	68070	GE1137951	endopeptidase inhibitor activity and plasminogen activator activity	- glucose homeostasis - many other biological processes; associated with diabetes Mellitus
FABP2	Adipocyte tissue	95478	134640	107	A_43_P11691	lipid transporter activity and fatty acid binding	Increase partitioning of glucose to triacylglycerols and enhance insulin resistance
PPAR-g	vascular smooth muscle cells, cells, endothelial adipocytes	97747	601487	7899	A_42_P462474	transcription factor activity	- Regulate lipid metabolic process - epithelial cell differentiation - regulation of fat cell differentiation - positive regulation of transcription
Aguti (AgRP)	Macrophages	892013	602311	7184	A_44_P257522	Receptor binding, neuro-peptide and hormone activity	Adult feeding behavior, neuro-peptide signaling pathway and hormone-mediated signaling
nSREBP-1		107606	184756	3079	rc_AI013042_at	transcription regulator activity	Regulation of lipid metabolic process, steroid metabolic process, cholesterol metabolic process and regulation of transcription
FOXO1	Adipose tissues	1890077	136533	1527	rc_AA893671_at	transcription factor activity	- Regulation of transcription - regulation of cell proliferation
11b-HSD-1	Visceral adipose tissue	103562	600713	68471		dehydrogenase activity and oxidoreductase activity	Lipid metabolic process
Apelin	Adipocytes	1353624	300297	8498	A_43_P12613	Hormone activity	- Plays a role in regulation of blood pressure - Stimulate gastric cell proliferation
Vaspin	Visceral adipose Tissue	891971	107400	20103	A_44_P288224	Hormone activity	regulates glucose tolerance and insulin sensitization

3.2. Second Phase (Databases Analysis)

The second phase of the research analyzes the gene orthologs and the gene ontology (**Table 2 and 3** respectively) of the 21 detected genes. The data pertaining to these genes/proteins obtained from the databases that are available online for free access.

4. DISCUSSION

The emerging epidemic of diabetes in Egypt and around the world cannot be ignored. According to the World Health Organization, over 180 billion people now have diabetes worldwide and this number is expected to double by the year 2030 (WHO, 2008). Similarly alarming is the high prevalence of two factors closely linked with increased risk for diabetes: Metabolic Syndrome (MetS) and obesity (Pradhan, 2007). Several recent studies investigated that, a number of common factors including genetic predisposition, poor dietary patterns, increased physical inactivity and longer life expectancy contribute to the rising prevalence of these disorders; subclinical inflammation may represent an additional novel risk factor. In this regard, epidemiologic data suggest that inflammatory biomarkers

may serve as important risk indicators for the future development of diabetes (Moller *et al*., 2003; Ford *et al*., 2004; Chew *et al*., 2006; Ogden *et al*., 2006; Shoelson *et al*., 2006; Ocana *et al*., 2010).

Also, there is growing evidence that the insulin-resistance syndrome associated to obesity is mainly caused by excessive accumulation of fat in intra-abdominal adipocytes (Macor *et al*., 1997; Kahn and Flier, 2000). It has been observed that the surgical removal of visceral fat improves insulin effect on hepatic glucose production in animal models of obesity (Barzilai *et al*., 1999). Adipose cells from visceral or subcutaneous depots largely differ concerning their metabolic characteristics as the control of lipolysis and the sensitivity to insulin (Wajchenberg, 2000). Therefore, it would be interesting to define the regional adipose differences in the expression of the recently discovered proteins, which are candidate links between fat accumulation and insulin resistance.

Complex traits such as obesity and type-2 diabetes pose special challenges for genetic analyses because of gene–gene and gene-environment interactions, genetic heterogeneity and low penetrance of the individual genes. The heterogeneity means that it is difficult to generalize genome scan results over different populations and ethnicities. In addition, the exponential and alarming growth of the obesity epidemic has led scientists to begin to take advantage of proteomics to identify obesity molecular targets and to study the mechanisms of action of potential obesity therapies. Proteomics analyses have been proven useful in the characterization of the adipocyte proteome (Adachi *et al*., 2007), in the identification of obesity targets in different models of experimental obesity and to characterize targets of several agents such as the insulin sensitizer rosiglitazone (Sanchez *et al*., 2003). Although they are highly informative, these strategies often generate large amounts of data and long lists of proteins that are difficult to analyze and understand their biological importance.

The approach in this article is similar to the one in Rao *et al*. (2008) and Park *et al*. (2009), but it is more robust to the data here, which are more heterogeneous and encompassing the bioinformatic gene analysis of human, mouse and rat models in addition to other variables.

The present bioinformatic analysis showed significant relationships between metabolic and obesity type-2 diabetes disease risk factors and abdominal subcutaneous adipose tissue gene expression.

Recently, You *et al*. (2005) investigated that, the quantity of visceral fat was negatively related to leptin and adiponectin abdominal adipose tissue gene expression. In addition, hyperinsulinemia, as indicated by fasting insulin and 2-h insulin during the Oral Glucose Tolerance Test (OGTT), was positively associated with adipose TNF-a and IL-6 gene expression. Also, Elbers *et al.* (2007) yielded an interesting list of candidate genes by investigating the overlapping chromosomal linkage regions for type-2 diabetes and obesity, using a combination of six computational disease gene identification methods. Many of these identified genes are excellent candidates to study further for their role in the shared disease aetiology between obesity and type-2 diabetes and a few have already been genetically or functionally associated with both disorders.

Current evidence supports that metabolic risk factors, including dyslipidemia, glucose intolerance and hyperinsulinemia, are linked with circulating levels of inflammatory and thrombotic cytokines (Chan *et al*., 2002; Bonora *et al*., 2003; Lyon and Hsueh, 2003). Relationships between cytokine gene expression in adipose tissue and metabolic risk and insulin resistance have been reported as well (Garaulet *et al*., 2004; Koistinen *et al*., 2000). Abdominal adipose gene expression levels of TNF-a (Koistinen *et al*., 2000), IL-6 (Rotter *et al*., 2003) and PAI-1 (Koistinen *et al*., 2000) are positively linked with insulin resistance and other cardiovascular risk factors, whereas adiponectin gene expression is negatively associated with metabolic variables (Garaulet *et al*., 2004). Our results were consistent with these previous findings and demonstrated that hyperinsulinemia was positively linked to adipose TNF-a and IL-6 gene expression and hyperinsulinemia and glucose intolerance were negatively linked to adipose adiponectin expression. Although these adipose-derived cytokines are traditionally viewed as the causes of the insulin resistance and metabolic risk (Rotter *et al*., 2003), recent evidence suggests that an elevated TNF-a and IL-6 expression (Krogh-Madsen *et al*., 2004) and a decreased adiponectin expression (Fasshauer *et al*., 2004) may also be a consequence of hyperinsulinemia. However, insulin infusion did not affect adiponectin gene expression in either healthy or type 2 diabetic individuals (Koistinen *et al*., 2004). Therefore, this study provides information from previous literatures and genome databases of different websites and act as a material for future studies to clarify the underlying mechanisms of these associations and finding of new therapies of obesity associated type2 diabetes mellitus.

5. CONCLUSION

In conclusion, any rigid assessment of disease patterns will need support from well documented and curated databases. However, there are also several practical and

theoretical constraints known if applying bioinformatics as a tool for improved understanding and diagnostics of disease patterns. So that, the current study provides evidence that the quantity of visceral fat and glucose/insulin complications of obesity is related to abdominal subcutaneous adipose tissue cytokine gene expression. Moreover, additional research is needed to discern whether abdominal subcutaneous adipocyte gene expression is causative for these risk factors or whether there is compensatory regulation of adipose tissue gene expression as a result of elevated visceral fat and/or insulin resistance.

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