Introduction

Osteoarthritis (OA) is the commonest degenerative joint disease that progressively results in loss of joint function and is the leading cause of physical disability and impaired quality of life ***(Honsawek et al., 2009).***

The cause of OA is not known; however, current evidence indicates that it is multifactorial. Major risk factors for OA are age, female sex, race, genetic factors, obesity, geographic factors, occupational knee-bending, physical labor, and joint trauma. Osteoarthritis causes joint pain, stiffness, and limitation of function. Knee involvement is the commonest presentation of this disease all over the world ***(Das and Farooqi, 2008).***

Obesity has long been considered a risk factor for OA ***(Englund and Lohmander, 2004)***. It has been reported that obesity increases the incidence of OA, particularly in weight-bearing joints such as knees ***(Felson et al., 1992)***, and weight reduction is correlated with decreased progression of OA. A prevailing hypothesis is that obesity increases mechanical loading across the articular cartilage, which leads to cartilage degeneration ***(Sharma and Chang, 2007)***. However, obesity also is associated with OA in non-weight-bearing joints such as finger joints, which suggests that metabolic factors contribute to the high prevalence of OA in obese subjects ***(Pottie et al.,2006)***.

Adipose tissue is a highly active endocrine organ. There has been growing evidence that the dominant cell type of adipose tissue, the adipocyte, has the ability to synthesize and release proinflammatory molecules, complement factors, signaling molecules, growth factors and adhesion molecules, suggesting an integrated function of adipocytes in tissue inflammation ***(Bokarewa et al., 2005).*** Among these molecules are Interleukin-6 (IL-6), macrophage migration inhibitory factor (MMIF), Tumor necrosis factor-α (TNFα), complement factor 3a, leptin, resistin and Adiponectin. For these molecules, the term "Adipocytokines" was introduced ***(Coppack, 2001)***. Among these adipokines, much attention has been paid to adiponectin's relationship with insulin sensitivity together with glucose and lipid metabolism. In addition, Adiponectin is known to exhibit potent atheroprotective ***(Matsuda et al., 2002)***, and antidiabetic effects***(Maeda et al., 2002)***.

Adiponectin has been considered as one of the adipokines implicated in OA pathogenesis, based on the following clinical observations: (a) plasma Adiponectin levels were significantly higher in OA patients than in healthy controls ***(Laurberg et al., 2009)***, and (b) higher plasma Adiponectin levels were observed in female patients with erosive hand OA than in those with nonerosive OA ***(Filková et al., 2009)***. In addition, Adiponectin has been detected in the OA synovial fluids, and its receptors are expressed in the joint tissues ***(Lago et al., 2008)***.

Adiponectin is a 244-amino-acid-long polypeptide. There are four distinct regions of Adiponectin. The first is a short signal sequence that targets the hormone for secretion outside the cell; next is a short region that varies between species; the third is a 65-amino acid region with similarity to collagenous proteins; the last is a globular domain. Overall this gene shows similarity to the complement 1Q factors (C1Q). However, when the 3-dimensional structure of the globular region was determined, a striking similarity to TNFα was observed, despite unrelated protein sequences ***(Shapiro and Scherer, 1998)***.

Adiponectin is a protein hormone that modulates a number of metabolic processes, including glucose regulation and fatty acid catabolism ***(Díez and Iglesias, 2003)***. Adiponectin is exclusively secreted from adipose tissue and also from the placenta in pregnancy ***(Chen et al., 2006)*** into the bloodstream where it accounts for approximately 0.01% of all plasma proteins at around 5-10 μg/mL. Levels of Adiponectin are reduced in diabetics compared to non-diabetics and are inversely correlated with body fat percentage in adults, ***(Ukkola and Santaniemi, 2002)*** while the association in infants and young children is less clear. Weight reduction significantly increases circulating levels ***(Coppola et al., 2008)***.

The hormone plays a role in the suppression of the metabolic derangements that may result in type2 diabetes ***(Ukkola and Santaniemi, 2002),*** obesity, atherosclerosis, ***(Díez and Iglesias, 2003)*** non-alcoholic fatty liver disease (NAFLD) and an independent risk factor for metabolic syndrome ***(Renaldi et al., 2009)***.

Aim of the Work

The aim of this study was to measure the serum level of Adiponectininpatients with primary kneeosteoarthritis in a trial to understand its role in pathogenesis of OA and to detect its value as a diagnostic and/or a severity marker for OA.

Adiponectin

1. Introduction:

Adiponectin is one of the adipocytokines (adipocyte-secreted hormone) known as gelatin-binding protein-28 (GBP-28), adipose most abundant gene transcript 1(apM1), adipocyte complement-related protein 30 (Acrp30), or AdipoQ. It is an adipose tissue specific collagen-like molecule described in 1996 that is produced mainly by white adipose tissue (WAT). It is expressed exclusively in adipocytes. It accounts for approximately 0.01% of total plasma proteins ***(Oh et al., 2007).***

It has been shown to have anti- diabetic, anti-sclerotic and anti-inflammatory functions. It is a protein which in humans is encoded by the ADIPOQ gene or apM1 gene, which is specifically and highly expressed in human adipose cells ***(Nedvidkova et al., 2005).***

2. Structure:

Adiponectin is a 244-amino-acid-long polypeptide with a molecular weight of approximately 30 kDa. The protein consists of four domains: one globular C-terminus, one collagen-like fibrous domain at the N-terminus (65-aminoacid region), one signaling peptide domain (short signal sequence that targets the hormone secretion outside the cell) and one

hypervariable domain that varies between species. However, when the 3-dimensional structure of the globular region was determined, a striking similarity to TNFα and complement factor C1q was observed, despite unrelated protein sequences ***(Whitehead et al., 2005).*** In plasma, full-length adiponectin combines via collagen domain and forms multimer complexes, such as trimers and hexamers, and a high-molecular-weight (HMW) form. A smaller form of adiponectin that consists of globular domain also exists in plasma in very small amounts ***(Okamoto et al., 2006).***

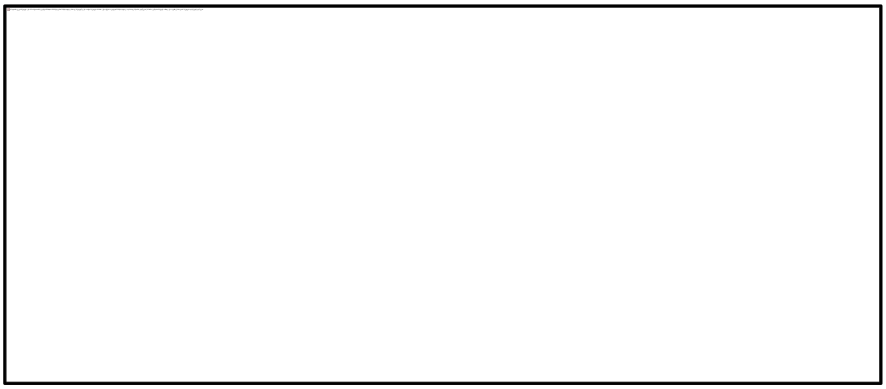

Figure (1): Domains and structure of adiponectin. HMW: High molecular weight ***(Okamoto et al., 2006).***

3. Synthesis:

Human adiponectin is encoded by the ADIPOQ gene (previously named apM1), which spans 17 kb on chromosome locus 3q27 ***(Takahashi et al., 2000).*** Interestingly, human chromosome 3q27 has been identified

as a region carrying susceptibility genes for type 2 diabetes and metabolic syndrome ***(Kissebah et al., 2000).***The human homologue was identified as the most abundant transcript in adipose tissue. Contrary to expectations, despite being produced in adipose tissue, adiponectin was found to be decreased in obesity***(Nedvídková et al., 2005).***

4. Circulatory multimeric forms:

Adiponectin is exclusively secreted from adipose tissue and also from the placenta in pregnancy ***(Chen et al., 2006))***into the bloodstream and is very abundant inplasmarelativeto many hormoneswith plasma levels in the µg/ml range, around three orders of magnitude higher than leptin***(Whitehead et al., 2005)***. Levels of the hormone are inversely correlated with body fat percentage in adults**.** While the association in infants and young children is less clear ***(Ukkola and Santaniemi, 2002).***

Adiponectin is secreted into the bloodstream where it accounts for approximately 0.01% of all plasma proteins. Plasma concentrations reveal a sexual dimorphism, with females having higher levels than males. Levels of adiponectin are reduced in diabetics compared to non-diabetics. Weight reduction significantly increases circulating levels ***(Coppola et al., 2008).***

Adiponectin automatically self-associates into larger structures. Initially, three adiponectin molecules bind together to form a homotrimer. The trimers continue to self-associate and form hexamers or dodecamers. Like the plasma concentration, the relative levels of the higher-order structures are sexually dimorphic, where females have increased proportions of the HMW forms. Some studies showed that the HMW form may be the most biologically active form regarding glucose homeostasis ***(Oh et al., 2007).***

Adiponectin can exist as full-length or a smaller, globular fragment; however, almost all adiponectin appears to exist as full-length adiponectin in plasma. It has been proposed that the globular fragment is generated by proteolytic cleavage, and recently it has been shown that the cleavage of adiponectin by leukocyte elastase secreted from activated monocytes and/or neutrophils could be responsible for the generation of the globular fragment of adiponectin ***(Waki et al., 2005).***

Oligomer formation of adiponectin depends on disulfide bond formation mediated by Cys-39 ***(Pajvani et al., 2003).*** Hydroxylation and glycosylation of the four lysines in the collagenous domain of adiponectin have been shown to play important roles in enhancing the ability of sub-physiological concentrations of insulin to inhibit gluconeogenesis in

hepatocytes ***(Wang et al., 2002)***. Adiponectin was reported to be a α2, 8-linked disialic acid-containing glycoprotein ***(Sato et al., 2001)***.

HMW adiponectin was further found to be associated with a lower risk of diabetes with similar magnitude of association as total adiponectin. However, coronary artery disease has been found to be positively associated with HMW adiponectin, but not with LMW adiponectin ***(Rizza et al., 2010).***

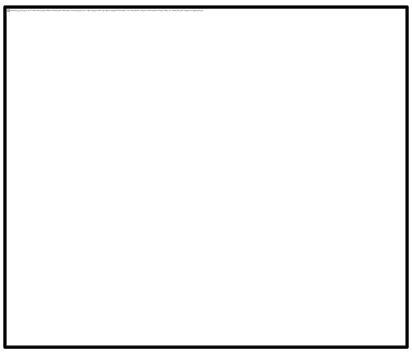

Figure (2): Multimer formation of adiponectin.

(HMW) High molecular weight, (MMW) Medium molecular weight, (LMW), low molecular weight and (S–S) disulfide bridge ***(Kadowaki and Yamauchi, 2005).***

5. Receptors:

Adiponectin binds to a number of receptors. So far, two receptors have been identified, with homology to G protein-coupled receptors and one receptor similar to the cadherin family.

1. Adiponectin receptor 1: Adipo R1.
6. Adiponectin receptor 2: Adipo R2.
7. T-cadherin: CDH13.

These have distinct tissue specificities within the body and have different affinities to the various forms of adiponectin. The receptors affect the downstream target Adinosine Mono Phosphate -activated protein kinase (AMP K), an important cellular metabolic rate control point ***(Bonnard et al., 2008).***

AdipoR1 and AdipoR2 appeared to be integral membrane proteins; the N terminus was internal, and the C terminus was external, which is opposite to the topology of all other reported G protein-coupled receptors. AdipoR1 and AdipoR2 may form both homo- and heteromultimers. AdipoR1 is a receptor for globular adiponectin and expressed mainly in skeletal muscles, whereas AdipoR2 is a receptor for full-length adiponectin and expressed mainly in liver ***(Yamauchi et al., 2003).***

The adiponectin receptors, AdipoR1 and AdipoR2 mediate increased AMPK and Peroxisome proliferator activated receptor alpha (PPAR-α) ligand activities, as well as fatty acid oxidation and glucose uptake by adiponectin ***(Yamauchi et al., 2003).***

Other studies showed that both AdipoRs and adiponectin were expressed in the human and rat brain and pituitary ***(Psilopanagioti et al., 2009).***

CDH-13, is a molecule that lacks the transmembrane and cytoplasmic domains and is bound to the surface membrane through a glycosyl phosphatidylinositol anchor. The expression of T-cadherin was observed to confer binding of hexameric HMW multimers but not trimeric adiponectin. It is also postulated that it may compete with AdipoRs for adiponectin binding or interfere with adiponectin signal transduction ***(Hug et al., 2004).***

HMW complexes of adiponectin were suggested to be a specific ligand for T-cadherin. Adiponectin binding to T-cadherin on vascular cells is associated with nuclear factor kappa B (NF-κB) activation ***(Hug et al., 2004).***

Regulation of Adiponectin Receptors:

The levels of AdipoR1 and AdipoR2 mRNA expression in the liver and skeletal muscle have been found to be increased after fasting, and refeeding rapidly restore these to levels equal to the original fed state. AdipoR1 and AdipoR2 mRNA increased significantly in skeletal muscle of mice rendered hypoinsulinemic/hyperglycemic with streptozotocin, and both

AdipoR1 and AdipoR2 mRNA were almost completely restored by insulin treatment ***(Bonnard et al., 2008).***

These observations suggest that insulin may negatively regulate AdipoR1/R2 mRNA levels. Expression of the receptors are correlated with insulin levels, as well as reduced in mouse models of diabetes, particularly in skeletal muscle and adipose tissue ***(Bonnard et al., 2008).***

Civitarese and his colleagues (2004), found that plasma adiponectin concentration were lower in people with a family history of type2 diabetes than in those with no family history of the disease and the expression levels of both receptors correlated positively with insulin sensitivity in non-diabetic Mexican Americans. ***Debard and his colleagues (2004),*** stated that adiponectin receptor expression in skeletal muscle of type 2 diabetic patients was also reported to be decreased.

Suppression of AdipoR1 with small interfering RNA (siRNA) reduces the increase in fatty-acid oxidation by globular adiponectin. Suppression of AdipoR2 with siRNA reduces the increase in fatty-acid oxidation by full-length adiponectin ***(Yamauchi et al., 2004).***

8.Function:

Adiponectin is a protein hormone that modulates a number of metabolic processes, including glucose regulation and fatty acid oxidation***(Díez and Iglesias, 2003).***

The hormone plays a role in the suppression of the metabolic derangement that may result in type 2 diabetes, obesity, atherosclerosis, non- alcoholic fatty liver disease (NAFLD) and an independent risk factor for metabolic syndrome (a cluster of abdominal obesity, dyslipidemia, hypertension and hyperglycemia) ***(Renaldi et al., 2009).***

Adiponectin in combination with leptin has been shown to completely reverse insulin resistance in mice ***(Yamauchi et al., 2001).***

Adiponectin exerts some of its weight reduction effects via the brain, this is similar to the action of leptin, but the two hormones perform complementary actions, and can have additive effects ***(Nedvidkova et al., 2005).***

1. Metabolic effects:***(Nedvidkova et al., 2005).***

1. Insulin sensitivity.
2. Glucose flux:

1. Decreased gluconeogenesis.
2. Increased glucose uptake.

1. Lipid catabolism:

1. B-oxidation.
2. Triglyceride clearance.
3. Weight loss.
4. Control of energy metabolism.

Adiponectin may regulate metabolism and insulin sensitivity through different mechanisms:

1. Promoting the phosphorylation and activation of AMPK in skeletal muscle, liver and adipocytes**.** AMPK signaling affects many aspects of cellular metabolism including glucose uptake, glucose utilization and fatty acid oxidation. AMPK causes glucose transporter type 4 (GLUT4) translocation to the cell surface to accelerate glucose uptake ***(Li et al., 2005),*** phosphorylation of phosphofructokinase-2 to enhance glycolytic disposal of glucose ***(Marsin et al., 2000).***

2. AMPK activation is believed to be mediated by adiponectin binding to the cell surface receptors AdipoR1 and AdipoR2 ***(Yamauchi et al., 2003)***.

3. TNF- α is one of the candidate molecules responsible for causing insulin resistance. The expression and secretion of adiponectin from adipocytes is significantly reduced by