Alterations in adiponectin concentration in hyper- and hypothyroid patients; possible underlying mechanisms & role of metformin treatment in experimental animals

Thesis
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(Basic Medical Sciences)

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Dedicated to

My beloved husband

My children Omar & Maram

My Parents, Brothers & Sisters

For their support & patience
Abstract

A more complete understanding of the interplay between adiponectin secretion, THs and metformin treatment will likely lead to better approaches for the management of thyroid disorders, type 2 diabetes, obesity, atherosclerosis and cardiovascular diseases.

In the current study we tried to investigate the interference between the thyroid status and serum adiponectin concentration, assess the possibility of involvement of adiponectin (through gC1q-R) in the regulation of thyroid hormone production in thyroid gland tissue, clarify the role of pituitary-thyroid axis in the modulation of adiponectin production from the adipose tissue and to assess the interplay between metformin treatment (used commonly for the treatment of diabetes), thyroid function and adiponectin formation.

Key words;

- Adiponectin
- TSH receptor
- PPARγ receptor
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LIST OF ABBREVIATIONS

Acrp 30 : Adipocyte complement-related protein
AdipoR 1 : Adiponectin receptor 1
AdipoR 2: Adiponectin receptor 2
Alb-LMW : Albumin bounded low molecular weight
ALT : Alanine aminotransferase
AMPK : Adenosine monophosphate-activated protein kinase
ANOVA: Analysis of variance
apM1 : Adipose most abundant gene transcript
BAT : Brown adipose tissue
BBB : Blood brain barrier
BMI: Body mass index
BMR : Basal metabolic rate
cAMP : Cyclic adenosine monophosphate
Cbfa1: Core binding factor alpha 1
CBP : cAMP binding protein
CCl4: Carbon tetrachloride
CO : Cardiac output
COX2 : Cyclooxygenase
D1 : Type I deiodinase
D2 : Type II deiodinase
D3: Type III deiodinase
DIT: Di-ioiodotyrosine
dNTPs: Deoxynucleotide triphosphates
DPP: Diabetes prevention program
ELISA: Solid phase enzyme-linked immunosorbent assay
eNOS: Endothelial nitric oxide synthase
fAPN: Full-length adiponectin
FFA: Free fatty acid
fT3: Free L-3,5,3'-triiodothyronine
fT4: Free L-3,5,3',5'-tetraiodothyronine
gAPN: Globular adiponectin
GBP 28: Gelatin-binding protein of 28 kDa
GFR: Glomerular filtration rate
GH: Growth hormone
GLP-1: Glucagon-like peptide-1
GPCRs: G protein-coupled receptors
GTC: Guanidine thiocyanate
H2O2: Hydrogen peroxide
HABP1: Hyaluronan binding protein 1
hCG: human chorionic gonadotropin
HDL: High-density lipoprotein
HIV: Human immune deficiency virus
HMG-CoA: 3-hydroxy-3-methylglutaryl-coenzyme A
HMW: High molecular weight
HOMA-IR: Homeostasis model assessment of insulin resistance
HPRI: Human placental ribonuclease inhibitor
IFN α: Interferon α
IGF-1: Insulin-like growth factor-1
IL: interleukin
KO: Knockout
LDL: Low density lipoprotein
LKB1: Liver Kinase B 1
Lp (a): Lipoprotein (a)
Lrp5: LDL receptor-related protein 5
MALA: Metformin-associated lactic acidosis
MAPK: Mitogen-activated protein kinase
MCT: Monocarboxylic acid transporters
MIT: Mono-iodotyrosine
MMLV: Moloney murine leukemia virus
MMW: Medium molecular weight
mTOR: Mammalian target of rapamycin
N-CoR: Nuclear receptor co-repressor
NEFA: Non-esterified fatty acid
NF-kB: Nuclear Factor Kappa Beta
NIS: Sodium-iodide symporter
NO: Nitric oxide
NPY: Neuropeptide Y
Oatps: Organic anion-transporting polypeptides
OD: Optical denisty
OVX: Ovariectomized
p27Kip1: Protein 27 cyclin-dependent kinase inhibitor 1B
p32/TAP: Protein 32/Tat-associated protein
PAI-1 : Plasminogen activator inhibitor-1
PCAF : P300/ cAMP binding protein -associated factor
PCOS : polycystic ovarian syndrome
PI3-K : Phosphatidylinositol 3-kinase
PKA : Protein kinase A
PPAR: Peroxisome proliferator-activated receptor
PVN: Paraventricular nucleus
qPCR: Quantitative polymerase chain reaction
RBF : Renal blood flow
RNase: Ribonuclease
RNS : Reactive nitrogen species
rT3: Reverse triiodothyronine
RT-PCR: Real time polymerase chain reaction
RXR : Retinoid X receptor
s.c.: Subcutaneous
SAT : Subcutaneous adipose tissue
SD: Standard deviation
SF2-associated p32 : Splicing factor associated protein 32
SiRNA : Small interfering RNA
Smad2 : mothers against decapentaplegic proteins 2
SMRT: Silencing mediator of retinoid and thyroid
SPSS : Statistical Package for the Social Science
SR: Sarcoplasmic-reticulum
**SRC-1:** Steroid receptor co-activator-1

**SREBP:** Sterol regulatory element-binding protein

**STAT3:** Signal transducer and activator of transcription 3

**SULTs:** Sulfotransferases

**T1:** Monoiodothyronamine

**T2:** 3,3’-diiodothyronine

**T2DM:** Type 2 diabetes mellitus

**T3:** L-3,5,3’- triiodothyronine

**T4:** L-3,5,3’,5’-tetraiodothyronine

**TC:** Total cholesterol

**TG:** Triglyceride

**Tg:** Thyroglobulin

**TGF-β:** Transforming growth factor β

**THs:** Thyroid hormones

**TMB:** Tetramethylbenzidine

**TNF-α:** Tumor necrosis factor-α

**tPA:** Tissue plasminogen activator

**TPO:** Thyroid peroxidase

**TRE:** Thyroid response elements

**TRH:** Thyrotropin-releasing hormone

**TRs:** Thyroid receptors

**TSH:** Thyroid stimulating hormone

**TSHr:** Thyroid stimulating hormone receptor

**UCP-1:** Uncoupling protein-1
**UCP-3**: Uncoupling protein-3

**UDPGTs**: Uridine diphosphate glucuronosyl transferases

**VAT**: Visceral adipose tissue

**VLDL**: Very low-density lipoprotein

**WAT**: White adipose tissue
Introduction

And

Aim of the work
INTRODUCTION & AIM OF THE WORK

Over the past decade and a half it has become increasingly clear that adipose tissue is a much more complex organ than was initially considered and that its metabolic functions extend well beyond the classical actions of thermoregulation and of storage and release of fatty acids. In fact, it is now well established that adipose tissue plays a critical role in maintenance of energy homeostasis through secretion of a large number of adipokines that interact with central as well as peripheral organs such as the brain, liver, pancreas, and skeletal muscle to control diverse processes, such as food intake, energy expenditure, carbohydrate and lipid metabolism, blood pressure, blood coagulation, and inflammation (Harwood, 2011).

Among these adipokines, Adiponectin is the most abundant produced by adipocytes. It is involved in a wide variety of physiological processes including energy metabolism, inflammation, and vascular physiology via actions on a broad spectrum of target organs (Vaiopoulos et al., 2012).

Adiponectin and thyroid hormones share some biological effects (Diez and Iglesias, 2009). Thyroid hormones act on several aspects of metabolic and energy homeostasis influencing body weight, thermogenesis, and lipolysis in adipose tissue. Adipocytokines, also have multiple effects on several tissues acting on the intermediate and energy metabolism (Iglesias and Diez, 2007). For these reasons, attention has recently been focused on the possible relationship between adipocytokines, thyroid status, and thyroid dysfunction.

Clinical studies examining adiponectin circulating levels of hypo- and hyperthyroid patients are not conclusive. It has been reported that serum adiponectin concentration was higher in hyperthyroid patients before treatment
than when they achieved a hypothyroid state in consequence of the treatment (Yaturu et al., 2004; Saito et al., 2005). Other studies found no changes in serum adiponectin concentration in thyroid dysfunctions (Iglesias et al., 2003; Santini et al., 2004).

Available experimental data suggest that adiponectin and thyroid hormones may interact with each other. Adiponectin may influence thyroid hormone production through interaction with gC1q receptor, whereas changes in the pituitary-thyroid axis may alter adiponectin levels. This could be either through PPAR pathway, adiponectin messenger RNA expression in the adipose tissue or TSH receptors in adipose tissue (Diez and Iglesias, 2009). Actually, there are no studies supporting these hypotheses.

Thyroid disorders and diabetes tend to coexist in a large number of patients (Hage et al., 2011). Metformin is a widely used drug for the treatment of type 2 diabetes (Schwartz et al., 2006; Bloomgarden, 2008). Recently it has been reported that metformin is able to interfere with thyroid hormone profile. Some studies reported a significant reduction in the serum levels of TSH following metformin administration (Vigersky et al., 2006; Isidro et al., 2007), but there are no enough reports that the drug modifies thyroid hormone economy and even the mechanism for this modification is still unclear. Metformin might affect adiponectin receptor expression (Metais et al., 2008) and consequently the pituitary-thyroid axis.

Several studies are still needed to explore the mutual roles of adiponectin and thyroid hormones and to clarify the influence of metformin treatment on the thyroid hormone economy.