THE EFFECT OF METFORMIN ON SERUM LEPTIN IN OBESE NIDDM

Thesis

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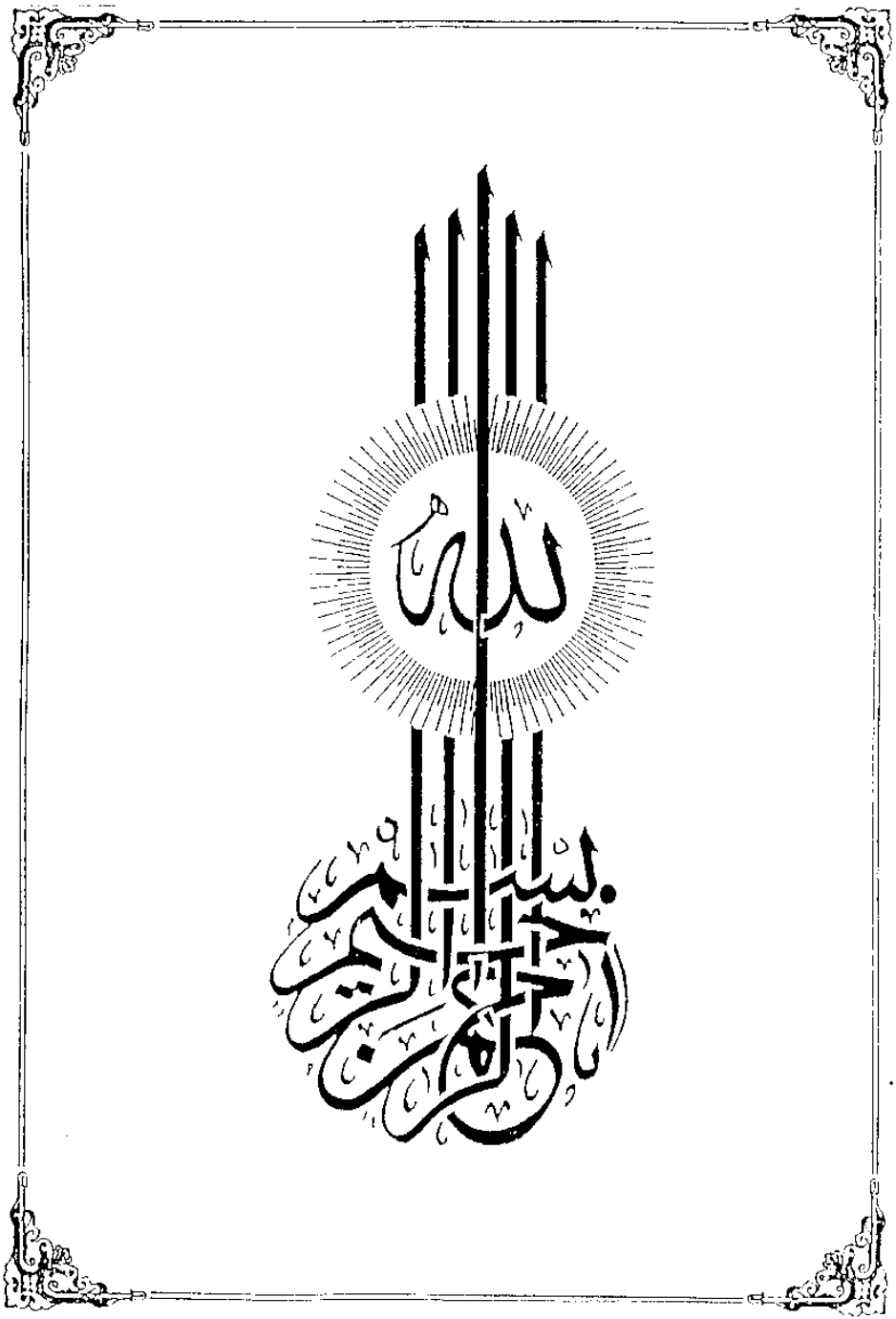

﴿ اللَّهُ نُورُ السَّمَوَاتِ وَالأَرْضِ مَثَلُ نُورِهِ كَمِشْكَاةٍ فِيهَا مِصْبَاحٌ الْمِصْبَاحُ فِي زُجَاجَةٍ الزُّجَاجَةُ كَأَنَّهَا كَوْكَبٌ دُرِّيٌّ يُوقَدُ مِن شَجَرَةٍ مُّبَارَكَةٍ زَيْتُونَةٍ لاَّ شَرْقِيَّةٍ وَلا غَرْبِيَّةٍ يَكَادُ زَيْتُهَا يُضِيءُ وَلَوْ لَمْ تَمْسَسْهُ نَارٌ نُّورٌ عَلَىٰ نُورٍ يَهْدِي اللَّهُ لِنُورِهِ مَن يَشَاءُ وَيَضْرِبُ اللَّهُ الأَمْثَالَ لِلنَّاسِ وَاللَّهُ بِكُلِّ شَيْءٍ عَلِيمٌ ﴾ .

صدق الله العظيم

Dedication

To the special people who always support and stand by me unconditionally because they care

Acknowledgement

Thank you Allah for what you have given me in my life for which I am so greatful and wish to make the best out of what I have.

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Last but not least, I keep all my good feelings for those who shared me alot of moments of success and can not be here today.

CONTENTS

ABBREVIATION LIST

ALT	: Alanine amino transferase.
AST	: Aspartate amino transferase.
BAT	: Brown adipose tissue.
BMI	: Body mass index.
ELISA	: Enzyme linked immunosorbent assay.
FBS	: Fasting blood sugar.
FSH	: Follicle stimulating hormone.
GLP-1	: Glucagon-like peptide 1.
GS	: Glycogen synthase.
HK	: Hexokinase.
HGP	: Hepatic glucose production.
IGT	: Impaired glucose tolerance.
ISPK-1	: Insulin stimulated protein kinase-1
JAK	: Janus kinase.
LH	: Leutinising hormone.
LHRH	: Leutinising hormone releasing hormone.
mRNA	: Messenger RNA.
NMR	: Neuromagnetic resonance.
NPY	: Neuropeptide Y.
PCOS	: Polycystic ovary syndrome.
PCR	: Polymerase chain reaction.
PDH	: Pyruvate dehydrogenase.

PFK : Phosphofructokinase.

PPAR-δ : Peroxisome proliferator activating receptor.

PP1 : Protein phosphatase type 1.

SI : Insulin sensitivity index.

STAT : Signal transducer and activator of transcription.

TG : Triglycerides.

UCP : Uncoupling protein.

W/H : Waist/hip ratio.

ABSTRACT

Leptin is the product of the human (ob) obese gene specific to the white adipose tissue and is one of the central regulators of body weight homeostasis. Metformin is an oral antidiabetic agent which by improving insulin sensitivity and decreasing hepatic glucose production improves the glycemic control.

Objective: Because leptin circulates at levels proportionate to body adiposity and because insulin may regulate leptin secretion and because NIDDM is a hyperinsulinemic insulin resistant state, we sought to determine if plasma leptin levels are coupled to body adiposity via changes in circulating insulin levels and whether leptin level is changed by metformin in obese NIDDM.

Research design and methods: Our case control study was conducted on 40 female subjects divided into 3 groups; 10 of which are lean, 10 obese non-diabetics and 20 obese NIDDM (who later received l500 mg daily meformin for 1 week and were told not to modify their diet).

Results: Fasting serum lepin was significantly higher in obese and obese NIDDM than lean women but no significant difference between serum leptin levels in NIDDM and obese non-diabetic subjects. Also a significantly positive correlation was found in all groups between the fasting serum leptin and the BMI ($P<0.00l$). While the fasting serum insulin was higher in obese NIDDM than obese and in the obese than the lean subjects, a significantly positive correlation in all groups was found between fasting serum leptin and insulin ($P<0.00l$). After 1 week of l500 mg daily metformin therapy in obese NIDDM a significant decrease in the leptin levels occurred inspite of a modest gain of 0.5 kg in body weight which was concomitant with improvement in the glycemic control end the decline in the fasting serum insulin.

Conclusions: We conclude that 1) Obesity is a hyperleptinemic, leptin resistant state. 2) Leptin secretion relates more to the extent of adiposity than to the degree of insulin resistance. 3) Insulin sensitivity contributes to the association between body adiposity and serum insulin levels and not leptin and is improved by metformin therapy. 4) Metformin therapy in obese (hyperleptinemic), insulin resistant NIDDM lowersserum insulin and leptin.

The mechanisms underlying the association between body adiposity, insulin resistance and circulating levels of these two hormones appear to be different yet indirectly related.