

**THE ROLE OF TUMOUR NECROSIS FACTOR
ALPHA (TNF α) IN OBESITY**



Alison Mary Morris, B.Sc (Hons)

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Department of Physiology
Adelaide University
South Australia

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TABLE OF CONTENTS

ABSTRACT	viii
DECLARATION	x
ACKNOWLEDGEMENTS	xi
GLOSSARY OF ABBREVIATIONS	xii
LIST OF FIGURES.....	xiv
LIST OF TABLES.....	xviii
PUBLICATIONS ARISING FROM THIS THESIS	xxi
CHAPTER 1: General Introduction.....	1
1.1 Overview	1
1.2 Obesity.....	1
1.2.1 The obesity epidemic	1
1.2.2 Defining obesity	3
1.2.3 Types of Obesity	3
1.2.4 Obesity related diseases	4
1.2.5 Determining Obesity	5
1.2.6 Benefits of weight loss in obesity	6
1.3. Insulin resistance and type II diabetes	6
1.3.1 Role of Insulin.....	6
1.3.2 Defining insulin resistance	7
1.3.3 How insulin resistance develops into type II diabetes	8
1.3.4 Molecular defects involved in Insulin Resistance	10
1.3.5 The Insulin Cascade	10
1.3.6 Risk factors for developing insulin resistance.....	11
1.3.6.a Disruptions to the GLUT4 glucose transport.....	12
1.3.6.b Disruptions to lipid metabolism result in insulin resistance	13
1.4 Adipocyte metabolism.....	14
1.4.1 Adipose tissue mass control	14
1.4.2 Lipogenesis and Lipolysis	14
1.5 Tumour Necrosis Factor-alpha (TNFα)	17
1.5.1 TNF α gene, protein and receptors	17
1.5.2 TNF α in obesity and insulin resistance	19
1.5.2.a Animal studies	19
1.5.2.b Human studies.....	21
1.5.2.b (i) Adipose tissue and skeletal muscle expression and secretion of TNF α ..	22
1.5.2.b (ii) Monocyte production of TNF α in human obesity	24

1.5.2.b (iii) Circulating levels of TNF α in humans	24
1.5.3 Polymorphisms in the TNF α promoter	26
1.5.4 Negative findings with TNF α neutralisation in humans	28
1.5.5 Actions of TNF α	29
1.5.5.a How does TNF α interfere with insulin signalling?	29
1.5.5.b The action of TNF α on enzymes involved in lipid metabolism	31
1.5.5.c Apoptosis induced by TNF α	32
1.5.5.d Indirect actions of TNF α	32
1.6 TNF α Receptors	34
1.6.1 Actions of the TNF α receptors	34
1.6.2 TNF α Receptors, obesity and insulin resistance.....	36
1.7 TNF α interacting with other adipocyte derived factors	37
1.7.1 Interactions between TNF α and other cytokines	38
1.7.2.Actions of TNF α on leptin production	39
1.7.3 Actions of TNF α on plasminogen activator inhibitor-1 (PAI-1).....	39
1.8 The action of TZDs on TNF α	41
1.9 Does TNF α have a pivotal role in limiting fat mass?.....	42
1.10 Summary and aims of the thesis	43
Chapter 2: General Methods.....	1
2.1 Study Design	1
2.1.1 Clinical Weight Loss Studies	1
2.1.2 Additional Subjects	1
2.1.3 Subjects recruited for weight loss studies.....	3
2.1.4 Inclusion Criteria.....	3
2.1.5 Dietary Information for Subjects.....	4
2.1.6 Diet Analysis for Weight Loss Studies.....	4
2.2 Study Protocol	5
2.2.1 Blood Sample Collection	7
2.2.2 Oral Glucose Tolerance Test (OGTT).....	7
2.2.3 Weight, waist circumference and height measurements.....	7
2.2.4 Blood pressure	8
2.2.5 Dual-energy X-ray absorptiometry for measuring Body Composition	8
2.3 Analysis of Blood Samples.....	9
2.3.1 Cobas-Bio Analysis.....	9
2.3.2 Insulin radioimmunoassay.....	9
2.4 Peripheral Blood Mononuclear Cell (PBMC) preparation.....	10

2.4.1 PBMC isolation	10
2.4.2 Cell Count and Incubation with TNF α secretagogue.....	10
2.4.3 Percentage of monocytes in cell suspension	11
2.5 Determining Production of TNF α from PBMC	11
2.6 Abdominal adipose tissue Biopsies	12
2.6.1 Biopsy procedure	12
2.7 RNA extraction	12
2.7.1 RNA extraction	12
2.7.2 RNA Quantitaion.....	13
2.8 Quantitation of TNF α mRNA	13
2.8.1 Reverse Transcription.....	13
2.8.2 PCR Amplification	14
2.8.3 Standard curve construction	18
2.9 Genomic DNA Extraction.....	18
2.10 TNF α <i>Nco</i> I Polymorphism.....	19
2.10.1 Amplification of genomic DNA	19
2.10.2 PCR Conditions	20
2.10.3 RFLP Analysis	21
2.11 Statistics.....	22
Chapter 3: <i>In vitro</i> production of TNFα by PBMCs.....	1
3.1 Introduction	1
3.1.1 TNF α production.....	1
3.1.2 Monocyte production of TNF α in type II diabetes.....	2
3.1.3 Monocyte production of TNF α in obesity	3
3.1.4 Monocyte production of TNF α with weight loss.....	4
3.1.5 Aim of this chapter	5
3.2 Methods	5
3.2.1 Subjects.....	5
3.2.2 PBMC stimulation by LPS	6
3.2.3 ELISA kit sensitivity	7
3.2.4 Statistics.....	9
3.3. Results	9
3.3.1 Diet Analysis.....	9
3.3.2 Weight loss and diet.....	10
3.3.3 Metabolic differences between non-diabetics and type II diabetics.....	11
3.3.4 Weight loss and the effects of diabetes and gender	12
3.3.4 Weight loss and changes in metabolic parameters	13

Variable	15
3.3.5 Dietary influence on TNF α production from PBMCs	15
3.3.6 Associations between TNF α production and obesity	15
3.3.7 Weight loss and TNF α production from PBMC.....	16
3.3.8 Correlations between TNF α and lipids	18
3.3.9 Correlations between plasma insulin and TNF α production	19
3.3.10 Correlations between plasma glucose and TNF α production from PBMCs.....	20
3.3.11 Correlations between SBP and TNF α production from PBMCs	21
3.4 Discussion	22
3.4.1 Monocyte production of TNF α in obesity and insulin resistance	22
3.4.2 The effect of obesity and weight loss on TNF α production by PBMCs	23
3.4.3 Associations with glucose and insulin and TNF α production from PBMCs.....	25
3.4.4 Different factors that could potentially affect TNF α production from PBMCs ...	26
3.4.5 Gender effects on TNF α production.....	27
3.4.6 Blood Pressure and TNF α	27
3.5 Critical Method Evaluation.....	28
3.5.1 Concentration of LPS used to stimulate PBMCs.....	28
3.6 Conclusion and Summary	29
Chapter 4: TNFα mRNA expression in adipose tissue	1
4.1 Introduction	1
4.1.1 TNF α mRNA expression in adipose tissue.....	1
4.1.2 Associations between TNF α mRNA expression in adipose tissue and obesity.....	1
4.1.3 Chapter Aim.....	3
4.2 Methods	3
4.2.1 Subject Characteristics	3
4.2.2 Fat Biopsies	4
4.2.3 Method of RNA extraction.....	4
4.2.4 Quality of RNA extracted	5
4.2.5 Statistics.....	5
4.3 Results	6
4.3.1 Diet Analysis.....	6
4.3.2 Weight loss and diet.....	7
4.3.3 Changes in metabolic parameters with weight loss	7
4.3.4 TNF α mRNA abundance in adipose tissue	10
4.3.5 Associations between TNF α mRNA expression and adiposity.....	12
4.3.6 Associations between TNF α mRNA abundance and metabolic variables	15

4.4 Discussion.....	17
4.4.1 How is adipose tissue TNF α mRNA abundance associated with obesity	17
4.4.2 Variations in TNF α mRNA expression in adipose tissue between subjects	18
4.4.3. Why does weight loss alter TNF α mRNA abundance in adipose tissue?	19
4.4.4 Associations between TNF α mRNA and metabolic parameters	20
4.5 Critical Method Evaluation.....	22
4.5.1 Adipose tissue biopsies.	22
4.5.2 Methods of quantifying mRNA	23
4.6 Summary and conclusion.....	25
CHAPTER 5: -308 NcoI TNFα RFLP	1
5.1 Introduction	1
5.1.1 Defining polymorphisms	1
5.1.2 Function of the -308 TNF α RFLP	3
5.1.3 -308 TNF α RFLP and obesity	3
5.1.4 Frequency of the -308 TNF α RFLP	5
5.1.5 Chapter Aims	5
5.2 Methods	6
5.2.1 Subjects.....	6
Smokers	6
5.2.1. (a) Subjects involved in weight loss studies	7
5.2.1. (b) Subjects recruited only for RFLP analysis	7
5.2.1. (c) Subjects in whom PBMC production of TNF α was also measured.....	7
5.2.1. (d) Subjects in whom TNF α expression in adipose tissue was also measured....	8
5.2.2 Statistics and Data Analysis.....	8
5.3 Results	10
5.3.1 Allele frequency	10
5.3.2 Baseline characteristics	12
5.3.3 Allele frequency of subjects involved in weight loss trials	15
5.3.4 Diet analysis based on genotype	15
5.3.5 Clinical and metabolic parameters during weight loss	16
5.3.6 Gender and diabetes status differences with weight loss	17
5.3.7 Associations with genotype and weight loss	19
5.4.8 Associations with genotype and systolic blood pressure	23
5.3.9 Differences in genotype grouping.....	23
5.3.10 TNF α production from PBMCs in relation to the NcoI RFLP	24
5.3.11 TNF α expression in adipose tissue in relation to the NcoI RFLP	24

5.3.12 Changes in percent total body fat and abdominal fat based on the <i>NcoI</i> RFLP	25
5.4 Discussion	26
5.4.1 Allele frequency	26
5.4.2 Associations between -308 TNF α RFLP and obesity	27
5.4.3 Weight loss and -308 TNF α RFLP	29
5.4.4 -308 TNF α RFLP associations with factors influencing syndrome X	30
5.4.5 -308 TNF α RFLP and TNF α production from PBMCs and mRNA expression	31
5.5 Conclusion	32
Chapter 6: General Discussion	1
6.1 Overview	1
6.2 Summary of findings	1
6.2.1 Associations between TNF α and obesity	3
6.2.2 How TNF α responds to weight loss	3
6.2.3 Associations of TNF α production with metabolic variables	5
6.2.3.a Blood Pressure	5
6.2.3.b Lipids	7
6.2.3.c Insulin	8
6.3 Implications	10
6.3.1 What is the main source of circulating TNF α ?	10
6.3.2 Clarifying the role of TNF α production by different tissues	12
6.3.3 TNF α and the interaction with other adipocyte derived factors	13
6.4 Limitations and suggestions for future directions of research	14
6.4.1 Other adipocyte derived factors	15
6.4.2 Other RFLPs in the TNF α gene which might be associated	16
6.5 Conclusion	16
A.1 Study foods tested	1
A.2 Example Subject Consent Form	2
A.3 Volunteer Information Sheet	3
B.1 Cell Culture Solution Preparation	1
B.1.1 Dextran T500- 6%	1
B.1.2 Counting Fluid for Mononuclear cell number determination	1
B.2 Molecular Biology Solutions	1
B.2.1 Loading Buffer recipe	1
BIBLIOGRAPHY	1

ABSTRACT

Tumour necrosis factor-alpha (TNF α) is an inflammatory mediator and has also been described as a possible factor in obesity related insulin resistance and type II diabetes, although a clear mechanism is still to be elucidated.

This thesis describes six randomised controlled dietary intervention trials that were performed in free living subjects, with the primary aim of inducing weight loss through moderate energy restrictive (~6000 KJ/day) diets of varying nutrient composition. Each study was 12 weeks in duration and all subjects involved were either overweight or obese. In all studies plasma lipids, glucose, insulin and blood pressure were measured before and after weight loss.

The first study, described in Chapter 3, involved measuring the production of TNF α by stimulated peripheral blood mononuclear cells (PBMCs), before and after weight loss, in obese type II diabetics and non-diabetic controls. There was a fall in production of TNF α with weight loss and this was more pronounced in males compared with females. There was no correlation between TNF α production and any measure of adiposity but there was a positive association between TNF α production and blood pressure.

In the second study (Chapter 4), TNF α mRNA expression in subcutaneous adipose tissue was measured using quantitative real time RT-PCR, both before and immediately after a 12 week period of caloric restriction, in obese non-diabetic women. As found with monocyte production of TNF α , there was no association between baseline TNF α mRNA expression and obesity but a positive association was observed with blood pressure. TNF α mRNA

abundance was not altered with weight loss. There was great variation in the effect of weight loss on TNF α mRNA expression, but overall there was a tendency for TNF α mRNA to be elevated ($p = 0.06$) following weight loss.

The presence of a functional polymorphism ($G \rightarrow A$) in the TNF α promoter at position -308 was determined in all of the subjects recruited for the six weight loss studies and an additional small number of obese subjects who did not undergo weight loss (Chapter 5). The TNFA allele in this Australian population was present at a frequency (0.21), which is comparable to other populations, but there was no difference between genotypes in initial BMI, the amount of weight lost (GG , $8.1 \pm 0.65\text{kg}$; AG , $6.9 \pm 0.77\text{kg}$; AA , $7.6 \pm 0.12\text{kg}$) or any metabolic variable.

In summary these studies show that the production of TNF α by PBMCs and expression by adipose tissue is not associated with obesity. Expression of TNF α in adipose tissue and monocyte production of TNF α respond differently to moderate weight loss. The association between TNF α expression and production and blood pressure is one that should be explored further. The disparate results between animal and human studies suggest that factors other than TNF α must also be involved in the metabolic changes associated with obesity.