Asian Journal of Immunology

Volume 8, Issue 1, Page 249-256, 2025; Article no.AJI.146139

Role of Tumour Necrosis Factor-Alpha and Adiponectin in Insulin Therapy Failure in Type 2 Diabetic Patients

Ayissi Marie-Ange [a], Biwole Sida Ghyslaine [b], Guiedem Elise [b,c], Yayah Emerencia Ngah [d,e], Jacky Bikio [b], Emilia Lyonga [b,f], Martha Messembe [b], Mispa Yivala Mbanyamsig [g] and Georges Ikomey [a,b,f*]

[a] Catholic University of Central Africa Yaounde, Cameroon.
[b] Faculty of Medicine and Biomedical Sciences, University of Yaoundé 1, Cameroon.
[c] Siantou Higher School of Health Sciences, Siantou University Institute, Cameroon.
[d] Department of Public Health, Faculty of Health Science, Texila American University, Zambia.
[e] Regional Hospital Bamenda, Cameroon.
[f] Cameroon Centre for the Study and Control of Communicable Diseases (CSCCD), FMBS, Cameroon.
[g] University of Skövde, Sweden.

Authors' contributions

This work was carried out in collaboration among all authors. Authors AM-A and GI were responsible for development of research concept, recruitment of patients, laboratory analyses, interpretation of results and participated in the initial drafting of the manuscript. Authors BSG, GE, YEN were responsible for development of research concept, interpretation of results and drafting of manuscript. Authors MM, EL, JB, and MYM contributed to the laboratory analyses and drafting of the manuscript. All authors read and approved the final manuscript.

Article Information

DOI: https://doi.org/10.9734/aji/2025/v8i1176

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://pr.sdiarticle5.com/review-history/146139

Short Research Article

Received: 18/08/2025
Published: 03/11/2025

**Corresponding author: E-mail: angeayissi04@gmail.com, mondinde@yahoo.com;*

Cite as: *Ayissi Marie-Ange, Biwole Sida Ghyslaine, Guiedem Elise, Yayah Emerencia Ngah, Jacky Bikio, Emilia Lyonga, Martha Messembe, Mispa Yivala Mbanyamsig, and Georges Ikomey. 2025. "Role of Tumour Necrosis Factor-Alpha and Adiponectin in Insulin Therapy Failure in Type 2 Diabetic Patients". Asian Journal of Immunology 8 (1):249–256. https://doi.org/10.9734/aji/2025/v8i1176.*

ABSTRACT

Background: Tumour necrosis factor alpha (TNF-α) and Adiponectin are both Pro and anti-inflammatory cytokines that play major roles in the pathogenesis and therapeutic management of many metabolic diseases.
Aim: This study aimed at evaluating the role of TNF-α and Adiponectin amongst Insulin-Treatment Failure and insulin therapy success in type 2 Diabetic Mellitus subjects using enzyme-linked immunosorbent assay (ELISA).
Methodology: The study was conducted at the Diabetic unit of the Cité verte hospital, Yaounde, Cameroon, between February 2023 and March 2024. A case-control study was conducted with 80 enrolled participants (41 insulin-treated patients with poor glycemic control and 39 patients with good glycemic control on insulin. The TNF-α, adiponectin and glycated haemoglobin were measured on whole blood specimens using immunoassay techniques. The Graph Pad Prism 5.0 and EPI Info 7.1. software was used for the analysis of data.
Results: TNF-α and Glycated haemoglobin (HbAIc) mean levels were higher in insulin-treated patients with poor glycemic control (TNF-α: 19.4 ± 8, HbAIc: 35.26 ± 11pg/ml) compared to patients with good glycemic control (TNF-α: 17.1 ± 6 pg/ml, HbAIc: 21.5 ± 5 pg/ml) with $p < 0.001$. The Adiponectin mean levels were lower in subjects with treatment failure (5.62 ± 4 pg/ml) compared to patients with treatment success (6.33 ± 6 pg/ml), was not statistically significant, p=0.0818. A negative correlation was observed between TNF-α and Adiponectin in subjects with treatment failure, with r=-0.03, which was not statistically significant, p=-0.08.
Conclusion: The variation of TNF-alpha and Adiponectin in uncontrolled patients on insulin therapy and well-controlled patients could justify their implications in the pathogenesis of type 2 diabetes. The increased levels of TNF-α, HbAIc, combined with the low levels of adiponectin, could be exploited as signalisation biomarkers for monitoring Insulin treatment failure and other metabolic dysregulation and inflammation.

Keywords: Type 2 diabetes; pro-inflammatory cytokines; insulin-treatment failure; insulin-treatment success; adiponectin.

1. INTRODUCTION

"Diabetes mellitus (DM) is a disease characterised by the disturbance of glucose homeostasis owing to insulin malfunction in the target tissues, causing abnormalities in fat, protein, and carbohydrate metabolism. The principal hallmark of the disease is an elevated glucose level in the venous plasma, which is the gold standard for the diagnosis of DM. The elevation of plasma glucose level is caused by absolute insulin deficiency, as in type 1 diabetes (T1DM), or increased insulin resistance, as in T2DM or both" (Emad-Eldin et al., 2024). "The management of insulin-treatment failure (ITF) in type 2 diabetes mellitus (T2DM) represents a major public health challenge worldwide. Despite regular insulin injections, many patients experience persistent hyperglycemia, frequent hypo- or hyperglycemic episodes, and unexplained weight fluctuations. One of the key mechanisms underlying these complications is chronic low-grade inflammation, which interferes with glucose metabolism and pancreatic β-cell function" (Beutler & Cerami, 1989; Hotamisligil et al., 1993; Hotamisligil, 2000). "Cytokines play a central role in this process. Pro-inflammatory cytokines such as tumour necrosis factor-alpha (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6) are consistently elevated in T2DM patients" (Chen et al., 2015; Bastard et al., 2002; Choi, 2016). "TNF-α, in particular, induces insulin resistance by disrupting insulin signalling pathways in peripheral tissues and promoting β-cell apoptosis through oxidative stress and endoplasmic reticulum dysfunction" (Lee & Lee, 2014; Wensveen et al., 2015; Shamsi et al., 2018).

"Adiponectin, is referred to as AdipoQ, APM1, or ACRP30, is composed of 244 amino acids, with a molecular weight of around 26 kilodaltons (kDa) secreted by white adipose tissue" (Yu et al., 2022). "These proteins are encoded by the AdipoQ gene and are located on the chromosome locus 3q27. They are secreted by adipose tissue, exerts protective effects by enhancing insulin sensitivity, stimulating lipid oxidation, and providing cardiovascular protection" (Sajid et al., 2018; Swaroop et al., 2012; Jeon et al., 2018). "Adiponectin exists in various isoforms— low, medium, and high

molecular weight—which exert their effects via receptors AdipoR1, AdipoR2, and T-cadherin, differentially expressed across tissues and immune cells. These distinct isoforms and receptor interactions underscore the complexity of adiponectin signalling and its broad spectrum of physiological effects" (Gianoli et al., 2025; Patel et al., 2021).

"However, reduced circulating levels of adiponectin are frequently observed in patients with obesity and T2DM, which contributes to the development of insulin resistance" (Liu et al., 2016; Matthews et al., 1985). "They cross-talk between adipocytes and immune cells, particularly macrophages, further aggravate this inflammatory state, creating a cycle of metabolic inflammation that fuels insulin resistance" (Van Dielen et al., 2004; Yudkin et al., 2000; Sartipy & Loskutoff, 2003). Glycated haemoglobin (HbA1c) is a measurement used for glycaemic control. The HbA1c was introduced into clinical use in the 1980s and subsequently has become a major guide for clinical practice.

Recent studies suggest that "the balance between pro-inflammatory cytokines (e.g., TNF-α) and anti-inflammatory adipokines (e.g., adiponectin) may serve as predictive markers for insulin therapy outcomes in T2DM" (Morris et al., 2006; Samad et al., 1997; Swaroop et al., 2012). The goal of this study was to evaluate the role of TNF-α and Adiponectin amongst Insulin-Treatment Failure (ITF) and success (ITS) T2DM subjects attending the Endocrinology unit of the clinical setting in a sub-Saharan African population Hospital, Cameroon.

2. MATERIALS AND METHODS

2.1 Study Design

The study was a case-control study with 80 participants enrolled between February 2023 and March 2024. All participants were consecutively recruited from the diabetic unit of the Cité verte hospital during daily routine consultation.

2.2 Study Population

The study population was made up of 80 diabetic patients divided into two groups: a group of patients with Insulin-Treatment Failure (ITF) consisting of 41 subjects as the case group and a group of 39 people with Insulin-Treatment Success (ITS) as the control group. The glycated haemoglobin (HbAIc) levels were considered for the selection of participants in the study. Specimens were aliquoted and stored at −80°C until ready to be used. Demographic data and clinical information were gathered for each participant through a standard questionnaire, which covered parameters like age, gender, insulin regimen, and duration of insulin treatment.

2.3 Sample Collection and Analysis Site

Five millilitres (5ml) of whole blood were collected, transported and analysed at the Centre for the Study and Control of Communicable Diseases (CSCCD) of the Faculty of Medicine and Biomedical Sciences (FMBS), University of Yaoundé I, Cameroon. Serum specimens were obtained by centrifuging whole blood at 5000 rpm for 5 minutes and subsequently stored in cryo-vals at -20°C. All samples were analysed within two months of collection to prevent cytokine degradation over time.

2.4 Laboratory Measurements

2.4.1 Measurement of TNF-α and adiponectin

TNF-α and Adiponectin were measured using quantitative sandwich Enzyme-linked Immunosorbent Assay (ELISA) kits from Invitrogen (Thermo Fisher Scientific, USA). A solid-phase Immune Enzymatic technique was employed on a microtiter plate for the quantitative determination of TNF-α and Adiponectin in human plasma. Samples were analysed according to the manufacturer's specifications. The absorbance was read using a spectrophotometer (Biotech ELx800, USA) set at a dual wavelength of 450-550 nm, with each sample run in duplicate. The concentration of both cytokines was determined by extrapolating the results from a standard curve generated by plotting the average absorbance (450-550 nm) obtained.

2.4.2 Measurement of glycated haemoglobin (HbA1c) using immune turbidimetry

Glycated haemoglobin was measured by Immunoturbidimetry using antibodies specific to HbA1c.The immunoturbidimetric instrument measured the changes in the sample. All the procedures as recommended by the manufacturer were respected.

2.5 Statistical Analyses

Data were analysed using the Graph Pad PRISM 5.0 software package (Graph Pad Software Inc.,

La Jolla, California, USA) and Epi Info 7.0 software (Epi Info™). Comparisons between TNF-α and Adiponectin within the various groups were conducted using the non-parametric Student's T-test. The correlations between TNF-α and Adiponectin were determined using Pearson's correlation coefficient. A significance level of $p < 0.05$ was considered statistically significant.

3. RESULTS AND DISCUSSION

3.1 Patient Characteristics

We enrolled 80 diabetic patients, of whom 65 % (n= 52) were females and 35 % (n= 28) males. Their mean age (± SD) was 56.89 ± 11.08 years. Patients were classified into two groups: Insulin Treatment Failure 51 %, n= 41, and Insulin Treatment Success 49 %, (n= 39).

3.2 Levels of TNF-α

The TNF-alpha levels were higher in ITF subjects compared to ITS subjects, with a mean ± SD of -0.1418±5 pg/ml, and -3.135±4 pg/ml, with p ≤0.001. The levels of glycated haemoglobin were higher in ITF compared to ITS, with a mean of 9.4 ±8 % and 6.37±6 %. The TNF-alpha levels were higher in ITF subjects compared to ITS subjects, with a mean ± SD of -0.1418±5 pg/ml, and -3.135±4 pg/ml, with p ≤0.001. The levels of Adiponectin were lower in ITF subjects compared to ITS subjects, with a mean ±SD of 5.62±4 pg/ml and 6.332±6 pg/ml, with p=0.081.

3.3 Levels of Adiponectin

Adiponectin concentrations varied between 1.60 and 8.97 pg/ml in ITF subjects, and from 2.252 to 10.51 pg/ml in ITS subjects (Fig. 2). This study revealed relatively lower levels of adiponectin in insulin-treated subjects than in our controls, but with a statistically non-significant difference (p=0.0818). The levels of glycated haemoglobin were higher in ITF compared to ITS, with a mean of 9.4 ± 8 % and 6.37±6 % respectively.

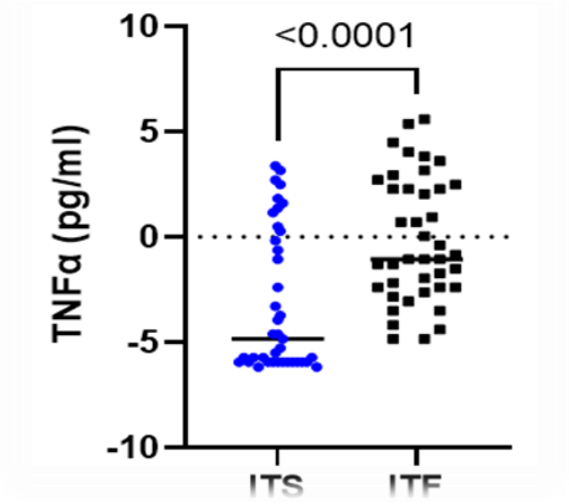

Fig. 1. The dot plot illustrates the plasma levels of TNF-α in insulin treatment failure and success groups

Table 1. The plasma levels of TNF-A and ADP in insulin treatment failure and success groups

Variable		ADP			TNF	
	ITF (Median) n=41	ITS (Median) n= 39	P	ITF (Median) n=41	ITS (Median) n=39	P
Sexe						
Female	5.94 (2.1-7.01)	6.50 (2.25-9.08)	0.79	-1.06 (-4.8 – (-5.31))	-4.83 (-6.17 - 3.15)	0.24
Male	5.90 (1.60- 8.48)	6.99 (2.5-10.5)	0.46	-0.73 (-4.17- 5.60)	-4.51 (-5.95 - 3.38)	0.32
Age						
[20-40]	5.873 (3.5-7.49)	/	/	-0.8406 (-3.5-5.37)	/	/
[41-60]	5.86 (1.60-8.48)	6.36 (2.93-10.5)	0.65	-2.06 (-4.84 - 5.6)	-5.17 (-6.18 - 3.38)	0.33
[61-80]	5.69 (3.7-8.97)	6.99 (2.25-9.08)	0.57	0.71(-3.51 - 4.49)	-5.06 (-5.95 - 2.49)	0.27

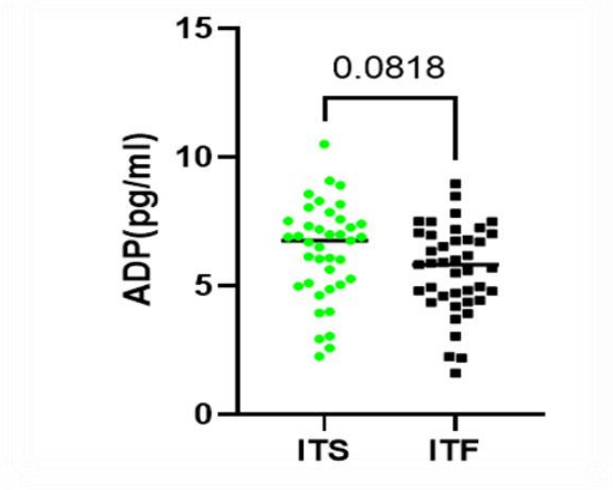

Fig. 2. The dot plot illustrates the plasma levels of ADP in insulin treatment failure and success groups

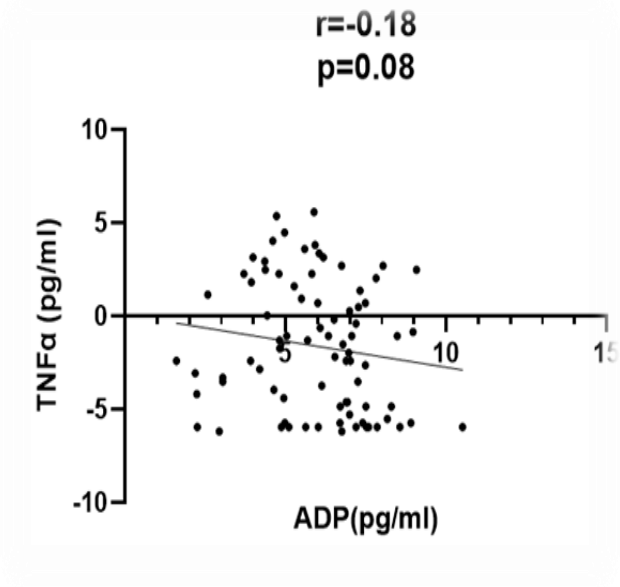

Fig. 3. Association between TNF-α and ADP in the general population study

3.4 Correlation between TNF-alpha and Adiponectin

There was a negative correlation between TNF-alpha and Adiponectin in ITF subjects, with r=-0.03 but non statistically significant p=-0.08. It is understood that within the two populations, for concentrations of TNF-alpha that evolve in an increasing way, we have concentrations of Adiponectin, which evolve in a decreasing Our results corroborate those of Chenxiao Liu et al. (2016), who found after a meta-analysis that the overall risk of T2DM is strongly associated with high levels of inflammatory cytokines, including TNF-alpha, and low levels of Adiponectin Showing that an interaction between inflammation and the development of T2 diabetes in subjects.

4. DISCUSSION

The results obtained show that the levels of TNF-alpha are significantly higher in ITF subjects, compared to ITS. Among other things, our results showed a significant difference between the two populations ($p \leq 0.001$); with concentrations varying between -4.838 and 5.600 pg/ml in ITF subjects and -6.170 to 3.379 pg/ml of blood in ITS subjects.

This is in line with the results of several scientific articles, which have also reported elevated levels of TNF-alpha in insulin-treated diabetics. According to the study by Shamsi et al. (2018), "TNF-alpha is associated with insulin resistance in these subjects". In addition, in the study conducted by Sajid et al. (2018) on "the role of TNF-alpha in the development of insulin resistance and the pathogenesis of T2DM, high levels of TNF-alpha have been shown to induce insulin resistance, which impairs insulin, contributing to the development of T2DM". Swaroop et al (2012) found "a positive but also significant correlation between TNF-alpha and HOMA IR (homeostasis assessment method to calculate insulin resistance) in T2DM subjects, suggesting an involvement of TNF-alpha in the development of insulin resistance. It is understood that within the two populations, for concentrations of TNF-alpha that evolve in an increasing way, we have concentrations of Adiponectin, which evolve in a decreasing way".

Our results corroborate those of Chenxiao Liu et al. (2016), who found after "a meta-analysis that the overall risk of T2DM is strongly associated with high levels of inflammatory cytokines, including TNF-alpha, and low levels of Adiponectin, showing that an interaction between inflammation and the development of T2DM". The results of this study also support the findings of Jeon et al. (2018), who evaluated "the level of Adiponectin in subjects with T2DM and healthy subjects, reporting a low concentration of adiponectin in subjects with type 2 diabetes".

The analyses also showed that there was an inverse ($r = -0.03$) and non-significant ($p = 0.82$) correlation between TNF-alpha and Adiponectin ITF subjects. Similarly, there is an inverse correlation between TNF-alpha and Adiponectin in non-insulin-treated subjects ($r= -0.08$), but this does not remain very significant ($p= 0.59$).

5. CONCLUSION

The increased levels of TNF-alpha, HbAIc, combined with the low levels of adiponectin, could be exploited as signalisation biomarkers for monitoring Insulin treatment failure and other metabolic dysregulation and inflammation. The variation of TNF-alpha and Adiponectin in the serum of Treatment Failure and non-failure Diabetic patients could justify their implications in the pathogenesis of type 2 diabetes and be a good predictive marker for its management.

CONSENT

All authors declare that written informed consent was obtained from the patients (or other approved parties) for publication of this study.

ETHICAL APPROVAL

All authors hereby declare that the study was conducted in accordance with ethical standards approved by the Cameroon National Ethics Committee, N° 2023/0220409/CEIRSH/ESS/MIM, and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of this manuscript.

ACKNOWLEDGEMENT

The authors thank the staff of the Cite vert Hospital and the Centre for the Study and Control of Communicable Diseases, Faculty of Medicine and Biomedical Sciences, University of Yaounde, Cameroon.

COMPETING INTERESTS

Authors have declared that they have no known competing financial interests or non-financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Peer-review history:
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