

Relationship Between Tumor Necrosis Factor Alpha, Adiponectin and Metabolic Parameters in Bantu Congolese at Brazzaville with and Without Insulin Resistance

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Abstract: *Back ground:* Tumor necrosis factor-alpha (TNF- α), adiponectin (ADP) and C-reactive protein (CRP) are associated with the risk of cardiovascular or non communicable diseases. *Aims:* To evaluate the association between TNF- α , ADP, CRP and metabolic markers in Congolese Bantu from Brazzaville. *Methods:* A cross-sectional case-control study was conducted during the period from July 2018 to February 2021. A total of 233 participants were recruited then divided into 130 healthy participants (control group) and 103 insulin resistant patients (case group). The Spearman correlation coefficient was calculated in order to search for an association between TNF α , ADP and the metabolic markers. An exponential nonlinear regression was used for the analysis of the association between TNF α (dependent variable) and CRP. *Results:* Participants were aged of 45.5 ± 13.1 years with a median BMI of 25.4 kg/m^2 , were included in this study. The median values of TNF α , CRP, ADP and HOMA-IR were 96.2 pg/mL , 12.3 mg/L , 8.6 ng/mL and 2.3 , respectively. TNF α was positively correlated with anthropometric parameters, CRP and insulin resistance. In contrast, ADP was negatively correlated with anthropometric parameters, CRP and insulin resistance. In control group, the equation was written as $\text{TNF } \alpha = 187 * (1 - 0.96^{\text{CRP}})$. The model shows that CRP explains 84.62% of the variability of TNF α in healthy participants. In case group, the equation was written as $\text{TNF } \alpha = 186.4 * (1 - 0.95^{\text{CRP}})$. The model shows that CRP explains 93.65% of the variability of TNF α in insulin-resistant participants. *Conclusion:* TNF alpha and ADP are associated at NC, WC, WHR, WHtR, LDL, CRP and insulin resistance in Congolese Bantu from Brazzaville.

Keywords: TNF Alpha, Adiponectin, Obesity, Insulin Resistance, Bantu, Brazzaville

1. Introduction

Tumor necrosis factor-alpha (TNF- α) is a pro-inflammatory cytokine produced by immune cells, including T lymphocytes. It is involved in the occurrence of several pathologies such as "salt-sensitive hypertension (SSH)" and its kidney damage [1], insulin resistance (IR), obesity and type 2 diabetes mellitus [2-4]. TNF α promotes hepatic production of C-reactive protein (CRP) [5], which is an acute phase inflammation protein [6]. TNF α and CRP are associated with the risk of developing chronic kidney disease in patients living with type 2 diabetes [7]. The objective of this study is to examine the relationship between TNF α , CRP, adiponectin (ADP) and metabolic markers in the Congolese Bantu of Brazzaville.

2. Methods

2.1. Nature, Period and Study Population

This is a cross-sectional case-control study conducted during the period from July 2018 to February 2021. A total of 233 participants were recruited. To verify the diagnosis of IR, the calculation of the "Homeostasis Model Assessment for Insulin Resistance" (HOMA-IR) was used, and the participants were then divided into 130 healthy participants (control group) and 103 insulin resistant patients (case group). All participants who were at least 18 years old and had given informed consent were included in the study. Exclusion criteria were: insulin treatment, recent or current

infection, personal history of cancer, and known dementia.

Participants had to come to the laboratory between 8:00 a.m. and 10:00 a.m. after a fasting night. A general somatic examination was performed. The arterial pressure in the supine arm after a 15-minute rest was measured. A tape measure applied to the skin was used to measure the circumference of the neck to the nearest 0.1 cm passing through the middle of the 0.5 cm below the laryngeal prominence. The waist measurement was taken, to within 0.1 cm, using a tape measure applied directly to the skin along the horizontal line passing between the iliac crest and the lower edge of the last floating rib. A blood sample was taken from an antecubital vein for biochemical analysis.

2.2. Biochemical Analyses

Blood samples, taken in glass tubes containing EDTA, were immediately centrifuged at the speed of 3500 x g for 15 minutes at 4°C. Plasma was isolated and stored at -21°C until analysis. Plasma concentrations of TNF α and ADP were measured by ELISA. In plasma, levels of blood glucose, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c), triglycerides (TG), CRP, uric acid and insulin were obtained by routine laboratory methods.

2.3. Definitions

The IR was defined by a value of HOMA-IR ≥ 2.5 .

The HOMA-IR was calculated by the following formula [8]:

$$\text{HOMA-IR} = [\text{insulin (mIU/L)} \times \text{fasting plasma glucose (mmol/L)}] / 22.5.$$

The Triglycerides-Glucose index (TyG index) [9] was obtained by the formula:

$$\text{TyG index} = \text{Ln} [\text{TG in mg/dL} \times \text{blood sugar in mg/dL} / 2].$$

Non-HDL was obtained by the difference between TC and HDL-c.

2.4. Statistical Analysis

Quantitative variables, normally distributed, were presented as means and their standard deviation. Quantitative variables with skewed distribution were presented as medians with their interquartile range. Qualitative variables were presented as proportions. Pearson's Chi-square test was used to compare proportions with application of Fisher's exact test and Yates' corrected test, where appropriate. Student's t-test was used to compare the means of two groups with normal distributions. Mann-Whitney's U test was applied in case of skewed distribution. In order to search for a possible association between TNF α , ADP and the other parameters, the Spearman correlation coefficient was calculated. An exponential nonlinear regression was used for the analysis of the association between TNF α (dependent variable) and CRP. SPSS version 26 and STATA version 14.0 software were used to analyze the data. The probability (p) value less than 0.05 (5%) was considered to be the level of statistical significance.

2.5. Ethical Considerations

All participants gave their free and informed verbal consent. This research work has been carried out in strict compliance with the recommendations of the Declaration of Helsinki III. The questionnaire was administered anonymously, and the information obtained during the interview / anamnesis and the clinical examination were transcribed into pre-established and pre-coded survey sheets while respecting the confidentiality and privacy of the participants. The study was approved by the ethics committee of the Lomo Research Center.

3. Results

3.1. General Characteristics of the Study Population

A total of 233 participants, aged 45.5 ± 13.1 years with a median BMI of 25.4 kg/m², were included in this study. The median atherogenicity index (TC/HDL-c), TNF α , CRP, ADP and HOMA-IR values were 2.6, 96.2 pg/mL, 12.3 mg/L, 8.6 ng/mL and 2.3, respectively. The TG/HDL-c ratio, the TyG index had an average value of 2.5 and 8.8, respectively. The insulin-resistant patients were older than those without IR ($p = 0.033$). Waist circumference (WC), neck circumference (NC), BMI, waist-to-height ratio

(WHtR), blood sugar, LDL-c, serum TG level, non-HDL-c, atherogenicity index, TG/HDL ratio -c, TyG index, TNF α as well as CRP were significantly higher in participants with

IR ($p < 0.01$). HDL-c and ADP were lower ($p < 0.001$) with IR. No significant difference in blood pressure, serum TC, and uric acid was observed in the two groups (Table 1).

Table 1. General characteristics of study population by metabolic status.

Variables	All (n=233)	IR(+) (n=103)	IR(-)(n=130)	p
Age, year	45.5 \pm 13.1	47.4 \pm 12.8	44.1 \pm 13.1	0.057
WC, cm	93.4 \pm 14.1	97.4 \pm 14.2	90.3 \pm 13.2	<0.001
NC, cm	36.5 \pm 3.0	37.2 \pm 2.8	35.9 \pm 3.0	0.001
BMI, kg/m ²	25.4 (8.3)	28.4 (7.7)	24.4 (5.8)	<0.001
WHR	0.90 (0.13)	0.91 (0.12)	0.89 (0.14)	0.299
WHtR	0.56 (0.12)	0.59 (0.11)	0.54 (0.13)	<0.001
SBP, mmHg	141.1 \pm 22.1	144.4 \pm 22.4	138.5 \pm 21.5	0.046
DBP, mmHg	88.1 \pm 13.7	89.3 \pm 12.9	87.1 \pm 14.3	0.221
FPG, mg/dL	86 (29.5)	101 (78)	81.0 (20.0)	<0.001
TC, mg/dL	160 (47)	160 (49)	160 (39)	0.465
HDL, mg/dL	66.3 \pm 18.1	57.7 \pm 15.1	73.1 \pm 17.3	<0.001
LDL, mg/dL	68.7 \pm 25.9	66.7 \pm 21.4	70.4 \pm 29.0	0.282
TG, mg/dL	154.0 \pm 41.5	173.5 \pm 35.3	138.5 \pm 39.6	<0.001
non-HDL, mg/dL	99.9 \pm 29.0	110.2 \pm 27.1	91.9 \pm 28.0	<0.001
TC/HDL	2.6 (1.2)	3.1 (0.8)	2.2 (0.7)	<0.001
TG/HDL	2.5 \pm 0.9	3.1 \pm 0.8	2.0 \pm 0.6	<0.001
TyG index	8.8 \pm 0.5	9.2 \pm 0.5	8.6 \pm 0.4	<0.001
TNF α , pg/mL	96.2 (97.3)	109.4 (76.9)	53.1 (87.7)	<0.001
CRP, mg/L	12.3 (21.4)	21.2 (22.6)	8.8 (13.1)	<0.001
ADP, ng/mL	8.6 (12.4)	8.0 (3.3)	10.9 (25.7)	<0.001
Physical activity				0.109
Inactive, n (%)	217 (93.1)	99 (96.1)	118 (90.8)	
Active, n (%)	16 (6.9)	4 (3.9)	12 (9.2)	
Socio-economic status				0.040
Low, n (%)	146 (62.7)	57 (55.3)	89 (68.5)	
Raised, n (%)	87 (37.3)	46 (44.7)	41 (31.5)	

No significant difference ($p > 0.05$) in TNF α , CRP, and ADP was observed between male and female participants (Table 2).

3.2. Correlations Between TNF α , ADP and Metabolic Parameters

In the control group, TNF α was positively correlated with WC, NC, BMI, waist-to-hip ratio (WHR), WHtR, CRP, TC,

TC/HDL and TG/ratio. HDL (Table 2). In contrast, ADP was negatively correlated with WC, NC, BMI, WHtR, WHR, CRP, TG, TG/HDL ratio as well as TyG index.

In the group of insulin-resistant participants, TNF α correlated positively with WC, NC, BMI, WHtR, WHR, CRP, and HOMA-IR. In contrast, ADP was negatively correlated with WC, BMI, WHtR, WHR, CRP and HOMA-IR (Table 3).

Table 2. Inflammatory markers of study population by sex.

Variables	All	Male	Female	p
TNF α , pg/mL	96.2 (97.3)	91.1 (94.3)	97.6 (104.2)	0.818
CRP, mg/L	12.3 (21.4)	12.0 (18.8)	12.3 (23.2)	0.791
ADP, ng/mL	8.6 (12.4)	8.7 (7.7)	8.5 (19.9)	0.681

Table 3. Correlation between TNF α , ADP and others parameters.

Variables	TNF α		ADP					
	Control		IR+		Control		IR+	
	Rho	p	Rho	p	Rho	P	Rho	p
Age	-0.043	0.625	-0.018	0.856	-0.021	0.810	-0.064	0.520
WC	0.377	<0.001	0.548	<0.001	-0.532	<0.001	-0.654	<0.001
NC	0.303	<0.001	0.256	0.009	-0.452	<0.001	-0.173	0.080
BMI	0.338	<0.001	0.300	0.002	-0.413	<0.001	-0.490	<0.001
WHtR	0.332	<0.001	0.432	<0.001	-0.444	<0.001	-0.593	<0.001
WHR	0.182	0.039	0.319	0.001	-0.168	0.056	-0.231	0.019
CRP	0.776	<0.001	0.761	<0.001	-0.712	<0.001	-0.383	<0.001
SBP	0.154	0.081	0.081	0.418	-0.177	0.044	-0.031	0.756
DBP	0.115	0.194	0.119	0.229	-0.097	0.270	-0.135	0.175
FPG	0.101	0.253	0.008	0.939	-0.152	0.085	-0.007	0.943
TC	0.182	0.038	-0.084	0.397	-0.141	0.109	-0.094	0.346
HDL	-0.054	0.540	0.031	0.759	0.052	0.560	-0.117	0.240

Variables	TNF α				ADP			
	Control		IR+		Control		IR+	
	Rho	p	Rho	p	Rho	P	Rho	p
TG	0.137	0.121	0.086	0.389	-0.259	0.003	-0.038	0.705
LDL	0.000	0.998	0.178	0.073	-0.067	0.449	-0.178	0.072
TC/HDL	0.218	0.013	-0.088	0.379	-0.147	0.095	0.055	0.581
TG/HDL	0.189	0.031	0.040	0.687	-0.261	0.003	0.043	0.667
HOMA-IR	0.168	0.055	0.201	0.042	-0.163	0.063	-0.237	0.016
TyG index	0.157	0.074	0.025	0.801	-0.271	0.002	0.103	0.299
Physical act.	-0.043	0.626	0.073	0.466	0.024	0.786	0.058	0.558
S.E. status	0.071	0.423	0.095	0.342	-0.194	0.027	-0.330	0.001

3.3. Relationship Between CRP and TNF α

An exponential nonlinear regression was conducted to investigate how CRP predicts TNF α . The model should be written as follows: $TNF\alpha = b1 * (1 - b2^{CRP})$. Table 4 shows

the coefficients of the regression with their confidence interval of the relationship between CRP and TNF α (dependent variable) in the control group.

Table 4. Non-linear regression between CRP and TNF α in the control group.

TNF α	Coef.	S.E.	t	p	95%CI	
b1	186.951	22.376	8.36	0.000	142.677	231.226
b2	0.959	0.008	117.53	0.000	0.943	0.975

Adj R² = 0.8462.

In participants without IR, the equation is written:

$$TNF\alpha = 187 * (1 - 0.96^{CRP}).$$

The model shows that CRP explains 84.62% of the variability of TNF α in healthy participants.

Table 5 shows the coefficients of the regression with their confidence interval of the relationship between CRP and TNF α (dependent variable) in the group of participants with IR.

Table 5. Non-linear regression between CRP and TNF α in the case group.

TNF α	Coef.	S.E.	t	p	95%CI	
b1	186.390	12.277	15.18	0.000	162.035	210.746
b2	0.948	0.007	126.20	0.000	0.933	0.962

Adj R² = 0.9365.

In participants with IR, the equation is written: $TNF\alpha = 186.4 * (1 - 0.95^{CRP})$. The model shows that CRP explains 93.65% of the variability of TNF α in insulin-resistant participants.

4. Discussion

This study reports the serum levels of TNF α , ADP and CRP in the Congolese insulin-resistant Bantu and in a healthy control group. Participants were carefully screened after ruling out any conditions that could interfere with TNF α , ADP, and CRP levels.

Observations of the incidence of coronary heart disease, in apparently healthy individuals with elevated CRP concentrations, have suggested the role of inflammation in initiating atherosclerosis as well as in precipitating acute events [10]. This study found higher serum CRP levels in insulin-resistant participants compared to the control group. Plomgaard *et al.* [11] reported similar results.

Several studies including that conducted by Yeo *et al.* [7] have shown that CRP as well as TNF α was independent risk factors for chronic kidney disease in patients with type 2

diabetes. The present study found serum levels of TNF α higher in the group of insulin-resistant participants. Kamil *et al.* [12] found similar results.

Several studies have shown that there is a gender difference in the production of pro-inflammatory cytokines. A study of more than 500 healthy blood donors showed that the production of pro-inflammatory cytokines (IL-1 β , IL-6, TNF α) released by monocytes after stimulation was higher in men, whereas women had higher production of lymphocyte-derived cytokines (IL-7, IL-22) [13]. Other investigators also reported that men had a higher production of monocyte-derived IL-1 β , IL-6 and TNF α upon stimulation [14, 15] and a decrease in the percentage of IL-2 producing lymphocytes compared to females [15]. The difference in ADP levels between the sexes may be due to androgen inhibition of ADP secretion in adipocytes [16]. Our study found that the levels of TNF α , ADP and CRP did not differ by sex in the Congolese Bantu. This could be explained by the relatively small size of the study population.

Our study found the association between TNF α , ADP, obesity (WC, NC, WHR and WHtR), the atherogenicity index and insulin resistance (TG/ HDL ratio, HOMA-IR) in

Bantu Congolese from Brazzaville. This corroborates the facts already established in the literature.

5. Conclusion

In low-resource countries, access to some biochemical tests including TNF α is not guaranteed for the majority of patients. The exponential nonlinear regression equations obtained in this study predict the level of TNF α from CRP. TNF α and ADP are associated at NC, WC, WHR, WHtR, CRP and insulin resistance in Congolese Bantu from Brazzaville. Further prospective studies are needed to explore the association of TNF α with the risk of developing degenerative complications in Bantu patients living with type 2 diabetes.

Conflict of Interest

The authors declare no conflict of interest.

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