

# The Plasma Levels of Protein Adiponectin (*AdipoQ*) and Meteorin-Like (*Metrnl*) in Newly Diagnosed Type 2 Diabetes Mellitus

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**Purpose:** This study aimed to measure the concentrations of the Adiponectin and Meteorin – Like (*Metrnl*) in newly diagnosed type 2 diabetes patients.

**Patients and Methods:** A comparative cross-sectional study contained two groups: Group 1 (86 newly diagnosed diabetes mellitus type 2 patients) and group 2 (71 healthy persons). The plasma concentrations of Adiponectin and *Metrnl* were measured by Enzyme Link Immunosorbent Assay (ELISA).

**Results:** The plasma level of Adiponectin of the newly diagnosed diabetes mellitus type 2 group and the healthy group were 1219.82 ng/mL (1132.43–2772.50) and 1187.25 ng/mL (1160.66–3807.50) respectively. The plasma level of *Metrnl* of two groups were 757.60 pg/mL (564.15–994.00) and 697.60 pg/mL (538.50–986.10) respectively. There were no significant difference between two groups. *Metrnl* had no correlation with glucose, HbA1c, lipid profile, BMI. Adiponectin had correlation with *Metrnl* and HDL-cholesterol. Adiponectin had no correlation to glucose, HbA1c, LDL-cholesterol, total cholesterol, triglyceride, BMI. People with the lower Adiponectin concentration had the higher risk of diabetes (OR=6.52; 95% CI: 2.43 –17.55).

**Conclusion:** Adiponectin and *Metrnl* were not significantly different in newly diagnosed type 2 diabetes and healthy people. The lower concentration of Adiponectin might increase the risk of type 2 diabetes.

**Keywords:** adipokine, insulin resistance, subfatin, adipo tissue, adipocyte - complement related protein of 30kDa, ACRP30

## Introduction

Adipose tissue is currently considered an endocrine gland in the body.<sup>1</sup> Adipokines derived from adipose tissue significantly impact metabolic activities in the body, primarily related to insulin resistance.<sup>2</sup> In the insulin resistance status field, some adipokines such as Adiponectin and *Metrnl* inhibit the resistance process. Otherwise, some adipokines increase insulin resistance, such as Resistin and Leptin.<sup>3–5</sup> *Adipoq* and *Metrnl* are two new adipokines found in 1990 years, and 2004.<sup>6,7</sup> Adiponectin may increase the insulin sensitivity, stimulate cell glucose uptake, glycolysis and oxidation, decrease the glucogenesis in liver.<sup>8–11</sup> Besides, adiponectin also against the inflammation and oxidation, and protect vascular cell.<sup>12,13</sup> Adiponectin was proven to be related to insulin resistance and some metabolic indexes such as weight and BMI.<sup>14,15</sup> *Metrnl* was found for the first time as a developing nervous cell factor by stimulating the neuroblast migration. Then, the homeostasis role in adipo tissue of *Metrnl* was proven. *Metrnl* simulates the transformation of white adipocyte into beige adipocyte, increases insulin sensitivity, lipid degeneration and anti<sup>16,17</sup> In recent years, Adiponectin and *Metrnl* played a supporting role in the action of drugs treating some metabolic diseases such as Sulfonylurea, Dapagliflozine...<sup>18,19</sup> Diabetes is a typical metabolic disease. The pathogenesis of diabetes has been proven to be related to obesity and insulin resistance. Many researchers have focused on the changes in the two proteins and the polymorphism of the gene in diabetes, the levels of two proteins, Adiponectin and *Metrnl*, and the relationship

with some diabetes risk, which were very different.<sup>20–23</sup> So, this study aimed to offer more insights into the concentrations of Adiponectin and Metrn1 in T2DM in a Vietnamese population.

## Materials and Methods

### Study Design

This study was a comparative cross-sectional – study containing 157 subjects enrolled in Hospital 103 from April 2022 to December 2023. A total of 157 subjects were divided into two groups. Group 1 (case group) contained 86 newly diagnosed type 2 diabetes mellitus and group 2 (control group) contained 71 healthy people of the same age. The inclusion criteria for the case group were: patients newly diagnosed with type 2 DM based on the American Diabetes Association criteria 2022.<sup>24</sup> The exclusion criteria for the case group were: type 1 DM, endocrinological disorder diseases such as thyroid disease; chronic kidney disease; chronic liver diseases; cancer; type 2 DM having treatment; and type 2 DM having complications, anemia, hemoglobinopathies such as thalassemia and B12 deficiency. The control group was chosen from healthy persons after a routine health check in the hospital having a similar age to the case group.

### Data Collection

The clinical characteristic of the subjects were data in the hospital admission. The fasting time of the subjects was at least 9 hours. The Heparin and EDTA blood sample were collected to determine the biochemistry indexes. The concentration of the glucose, urea, creatinine, total cholesterol, HDL-cholesterol, LDL-cholesterol, triglyceride, uric acid were determined in the AU5800 system with the colorimetric method (Beckman Coulter, USA). The HbA1c were qualified by the high performance liquid chromatography (HPLC) method in the Premier 9201 (Trinity Biotech, USA). The insulin was determined by the chemiluminescent immunoassay (CIA) in the DXI 800 (Beckman Coulter, USA).

The plasma separated from the Heparin blood tube were collected, then stored at the –20 degree Celcius. The plasma were used to determine the levels of the two protein Adipoq and Metrn1. The principle of quantities of the two protein was sandwich Enzyme Link Immunosorbent Assay (ELISA) with the human Adiponectin reagent kit and the human Metrn1 reagent kit (MyBioSources, USA).

The body mass index (BMI) was calculated as the ratio of weight divided for the square of height. The insulin resistance index was calculated based on some metabolic factors with the formula:

TyG index (Triglyceride Glucose Index) =  $\ln[(\text{fasting triglyceride level (mg/dl)} \times \text{fasting glucose level (mg/dl)})/2]$ .<sup>25</sup>

METS-IR (Metabolic Score for Insulin Resistance) =  $\ln [(2 \times \text{fasting glucose level (mg/dl)} + \text{Triglyceride (mg/dl)}) \times \text{BMI}]/(\ln [\text{HDL-c (mg/dl)}])$ .<sup>26</sup>

### Ethical Consideration

All patients provided informed consent, in accordance with the Declaration of Helsinki. This study was approved by the Hanoi Medical University Institutional Ethical Review Board with reference number 686/GCN-HĐĐĐNCYSH-ĐHYHN on date 06 April, 2022.

### Statistic Analysis

The data were recorded on the Microsoft excel 2013 and analysis by SPSS 22.0. The qualitative variables in normal distribution were presented by mean and standard deviation. The qualitative variables in abnormal distribution were presented by median and interquartile range. The differences between the means of the groups were calculated by the Man-Whitney's test or the *t*-test depending on the distribution. The results were considered to be significant with  $p < 0.05$ .

The Adiponectin and Metrn1 levels were categorized by median and inter quartile range (IQR). The unadjusted binary logistic regression analysis was used to identify the risk factors for diabetes. The odds ratios (ORs) and the corresponding 95% confidence intervals (95% CI) were calculated using the logistic regression model.

**Table 1** The Characteristic of the Subjects

	<b>Group 1 (T2DM group) n= 86</b>	<b>Group 2 (Control group) n = 71</b>	<b>p - value</b>
Age (Mean $\pm$ SD, year)	55.64 $\pm$ 11.42	54.39 $\pm$ 8.34	0.45
Gender (n, %)			
Male	32 (37.21)	49 (69.01)	
Female	54 (62.79)	22 (30.99)	
Duration of clinical symptoms (Mean $\pm$ SD, months)	3.4 $\pm$ 0.7	-	
BMI (Mean $\pm$ SD)	24.04 $\pm$ 3.32	21.76 $\pm$ 1.78	< 0.01
Glucose (mmol/l)	11.60 $\pm$ 4.59	5.05 $\pm$ 0.42	< 0.01
HbA1c (%)	9.37 $\pm$ 2.21	5.67 $\pm$ 0.29	< 0.01
Ure (mmol/l)	5.51 $\pm$ 1.42	4.77 $\pm$ 1.08	0.01
Creatinine ( $\mu$ mol/l)	80.39 $\pm$ 15.33	72.44 $\pm$ 10.81	< 0.01
Cholesterol (mmol/l)	5.82 $\pm$ 1.19	4.95 $\pm$ 0.79	< 0.01
HDL-cholesterol (mmol/l)	1.18 $\pm$ 0.27	1.30 $\pm$ 0.23	0.02
LDL-Cholesterol (mmol/l)	3.60 $\pm$ 0.80	3.01 $\pm$ 0.62	< 0.01
Triglyceride (mmol/l)	3.46 $\pm$ 3.00	1.46 $\pm$ 0.69	< 0.01
AST (U/L)	28.00 $\pm$ 19.96	24.10 $\pm$ 7.14	0.12
ALT (U/L)	30.19 $\pm$ 15.78	19.89 $\pm$ 8.54	0.01
TyG index	5.39 $\pm$ 0.41	4.64 $\pm$ 0.24	< 0.01
MET-IR	41.78 $\pm$ 7.58	32.22 $\pm$ 3.25	< 0.01

**Notes:** p value was significant at 0.05.

**Abbreviations:** T2DM, type 2 Diabetes Mellitus; BMI, body mass index; SD, standard deviation; HDL, high density lipoprotein; LDL, low density lipoprotein; AST, aspartate transaminase; ALT, Alanine Transaminase; MET-IR, Metabolic Score for Insulin Resistance; TyG index, Triglyceride Glucose Index.

## Results

### The Subject's Characteristics

Some clinical and laboratory indexes of the subjects were shown in [Table 1](#). The differences between the two groups in BMI, plasma glucose, urea, creatinine, triglyceride, cholesterol, HDL-cholesterol, LDL-cholesterol, ALT, METS-IR and TyG index were significant with  $p < 0.05$ . There was no difference in AST.

### The Plasma Concentrations of the Adiponectin and Metrn1

The median and interquartile range of the Adiponectin level of group 1 and 2 were 1219.82 ng/mL (1132.43–2772.50) and 1187.25 ng/mL (1160.66–3807.50) respectively. The median and interquartile range of the Metrn1 level of group 1 and 2 were 757.60 pg/mL (564.15–994.00) and 697.60 pg/mL (538.50–986.10) respectively. There were no differences in the plasma concentration of Adiponectin and Metrn1 between two groups ([Table 2](#)).

### The Correlation Between the Two Protein Level and Some Clinical Characteristics

The plasma level of Adiponectin had correlation with the plasma level of Metrn1 and HDL-cholesterol. There was no correlation between the plasma level of Adiponectin and Metrn1 with the level of Glucose, Cholesterol, Triglyceride, LDL-cholesterol, HbA1c and TyG index, MET-IR. ([Table 3](#)).

**Table 2** The Plasma Levels of the Adiponectin and Metrnl

	Group 1 (T2DM group) n= 86	Group 2 (Control group) n = 71	p - value
<b>Adiponectin (ng/mL)</b> <b>Median</b> <i>Inter quartile range</i>	<b>1219.82</b> <i>1132.43–2772.50</i>	<b>1192.63</b> <i>1162.83–3952.50</i>	<i>0.07</i>
<b>Metrnl (pg/mL)</b> <b>Median</b> <i>Interquartile range</i>	<b>757.60</b> <i>564.15–994.00</i>	<b>706.40</b> <i>565.40–1000.80</i>	<i>0.79</i>

**Notes:** p value was significant at 0.05.

**Abbreviations:** T2DM, type 2 Diabetes Mellitus; Metrnl, Meteorin – Like.

**Table 3** The Correlation Between the Plasma Levels of Adiponectin and Metrnl with Some Clinical and Laboratory Index

	Glu	Hb	Metrnl	METS-IR	TyG	Cho	HDL	LDL	Try	BMI
<b>Adiponectin</b>	–0.075	–0.029	0.238*	–0.135	–0.155	0.085	0.282*	0.102	–0.127	0.08
<b>Metrnl</b>	–0.096	–0.072	-	–0.096	–0.112	–0.075	0.132	–0.062	–0.097	0.053

**Notes:** \* The correlation is significant at the 0.05 level (2-tailed).

**Abbreviations:** Glu, Glucose; Hb, HbA1c; Cho, Total Cholesterol; HDL, HDL-cholesterol; LDL, LDL-cholesterol; Try, Triglyceride; BMI, body mass index; MET-IR, Metabolic Score for Insulin Resistance; TyG index, Triglyceride Glucose Index, Metrnl: Meteorin – Like.

**Table 4** Odd Ratios for Incident of Diabetes by Quartile of Adiponectin and Metrnl

	Q1	Q2	Q3	Q4	p Trend*
<b>Adiponectin</b>	1.00	6.52 (2.43 –17.55)	1.40 (0.53–3.71)	3.04 (1.30–8.79)	< 0.001
<b>Metrnl</b>	1.00	1.36 (0.55–3.31)	0.73 (0.30–1.79)	0.99 (0.40–2.41)	0.49

**Notes:** \* The correlation is significant at the 0.05 level (2-tailed).

**Abbreviations:** Q, Quartile; Metrnl, Meteorin – Like.

## The Odd Ratio of Type 2 Diabetes Evaluated by the Adiponectin and Metrnl Level

The odds of type 2 diabetes in the total study population were evaluated by multivariate logistic regression analysis (Table 4). The Adiponectin level and Metrnl level were divided by quartiles, with the lowest quartiles being the reference quartiles. The lower level of Adiponectin was significantly associated with the higher odds of type 2 diabetes ( $p < 0.05$ ).

## Discussion

Insulin resistance has become the primary mechanism of many diseases, such as metabolic syndrome, diabetes, and cardiovascular disease. The decrease in the insulin signal in target cells caused all the symptoms or complications of these diseases. The main therapeutic method nowadays is insulin injection or other methods for simulating insulin signals. The endogenous substances are always a priority in researches. In the adipose tissue, Adiponectin and Metrnl have a role in increasing insulin sensitivity through many signals. Most importantly, both adipokines activated the peroxisome proliferator-activated receptor- $\alpha$  (PPAR $\alpha$ ) signal.<sup>11,17</sup> The PPAR $\alpha$  signal increases the fatty acid oxidation to decrease the triglyceride concentration in blood, the lipid accumulation in the body.<sup>27</sup> In vivo experiments, Metrnl was proved to be the transcript factor in different adipocytes and lipid metabolism genes such as transferring and degeneration. Metrnl activated the expression and action of lipase in the blood.<sup>28</sup> Conversely, both adipokines activate the AMP-activated protein kinase (AMPK), which inhibits Acetyl Coenzyme A Carboxylase (ACC) and promotes fatty acid oxidation. AMPK also stimulates the Glucotransporter 4 (GLUT4) translocation that increases glucose absorption in muscle.<sup>29</sup> So, Adiponectin and Metrnl might have an impact on lipid and glucose control, increasing insulin sensitivity.

These adipokines also inhibit some inflammatory and macrophages, which are causative and aggravating factors in metabolic diseases.<sup>28,30</sup>

Many studies were designed to compare the concentration of two proteins within many groups at many stages of diabetes containing normal glucose intolerance, impaired intolerance, the onset of diabetes (the newly diagnosed), and diabetes. The results showed a decreasing concentration of two proteins in the diabetes group. The concentrations differed within the intolerance and newly diagnosed phase research. Some researchers found a lower level in the impaired intolerance group and newly diagnosed group than in the normal intolerance group. A community study on 3680 individuals in Japan showed that Adiponectin concentrations gradually decreased from the healthy group to the pre-diabetic group to the diabetic group.<sup>31</sup> The others and our researchers showed inverse results. Research in China on 405 individuals showed that in the pre-diabetic group, Adiponectin concentrations increased higher than in the healthy and diabetic groups.<sup>32</sup> With the Metrn1, the results were also controversial.<sup>20,33</sup> A meta-analysis indicated no significant change in circulating Metrn1 levels in T2DM patients.<sup>21</sup> Our study showed no differences in the concentration of two proteins between the newly diagnosed diabetes group and the healthy control group. Based on the results from research, changes in the concentrations of these adipokines might occur according to the stage of disease development. It could also be speculated that in the pre-diabetes stage, Adiponectin and Metrn1 levels may increase as a reaction to oppose the pathways leading to the disease. Specifically, it opposed insulin resistance and microscopic inflammation.<sup>34–36</sup> The concentration increase might continue long or short, depending on each person. At the disease stage, the concentration would have a downtrend. So, at the time of the collection of samples in our study, the concentration of the two proteins fluctuates.

In the diabetes group, the ALT was higher than in the healthy group. This status might associate to the insulin resistance in the hepa cells, and weight and lipid.<sup>37,38</sup> In recent research, the relationship between the Nonalcoholic fatty liver disease (NAFLD) and diabetes were mentioned and proved.<sup>39</sup>

In this study, the lower level of Adiponectin might increase about 6.5 times the risk of T2DM. This result was similar to some research. The Copenhagen General Population Study observationally determined the plasma adiponectin concentration in 1751 samples with type 2 diabetes. The results showed that the lower adiponectin associated with an increased risk of type 2 diabetes. In comparisons with individuals with median plasma adiponectin of 28.9 mg/mL (4th quartile), multivariable adjusted hazard ratios (HRs) for type 2 diabetes were 1.42 (95% CI 1.18–1.72) for 19.2 mg/mL (3rd quartile), 2.21 (1.84–2.66) for 13.9 mg/mL (2nd quartile), and 4.05 (3.38–4.86) for individuals with a median plasma adiponectin of 9.2 mg/mL (1st quartile).<sup>40</sup> In the research of Coltel et al containing 954 elderly high-cardiovascular risk Mediterranean subjects, the results showed that high plasma adiponectin was associated with lower type 2 diabetes risk in the whole population (OR = 0.61; 95% CI: 0.46–0.80;  $p = 4.4 \times 10^{-4}$ ).<sup>41</sup> The Adiponectin and Metrn1 were often determined with the immuno principle (ELISA or latex enhanced turbidimetric immunoassay) so that their concentrations were different and biased within the research. Besides, the concentration depends on many factors such as the different types of adipose tissue, inflammation status, physical activities, and race. However, we also found that there would be a relationship between the changes in adipokine and diabetes.

In the relationship to the clinical risk of diabetes, our study has shown that the concentration of Metrn1 did not correlate with glucose, HbA1c, lipid profile, or insulin sensitivity indexes. Adiponectin correlated the Metrn1 and HDL-cholesterol. Adiponectin did not correlate with the glucose, HbA1c, BMI, total cholesterol, triglycerides, LDL-cholesterol, and insulin sensitivity indexes. Although the correlation between Adiponectin and Metrn1 with the BMI, lipid profile, HbA1c, or glucose were found, the correlation coefficients were still weak. In the study of Coltell et al, Adiponectin had the correlation to HDL-cholesterol ( $r^2=0.391$ ), LDL-cholesterol ( $r^2=0.109$ ); BMI ( $r^2=0.029$ ).<sup>41</sup> In the research of Du et al, Metrn1 had no correlation to BMI, HDL, HbA1c, Glucose.<sup>42</sup> But in other researches of Wang et al and Ding et al, Metrn1 had week correlation to BMI, Triglyceride, LDL-cholesterol, HDL-cholesterol, HbA1c (all the coefficient factors were less than 0.5).<sup>33,43</sup>

The limitations of our study are: First, the study sample size is still small. Second, the concentration of these adipokines might affected by some factors such as diet, exercise, age, and gender.<sup>44,45</sup> Besides, the adipokines are derived from the adipose tissues so that the secretion might depend on the BMI and fat mass volume. In this research, we did not

estimate the red blood cell span, which is one of the most impacting factors on HbA1c results. We only used the Hemoglobin test to collect the subjects.

In terms of diagnostic value, these adipokines cannot be compared with classic tests in diabetes. However, it might contribute to assessing the risk of diabetes, or become a direction in improving insulin resistance and improving the manifestations of metabolic syndrome.

## Conclusion

Adiponectin and Metrnl were not significantly different in newly diagnosed type 2 diabetes and healthy people. The lower concentration of Adiponectin might increase the risk of type 2 diabetes.

## Disclosure

The authors report no conflicts of interest in this work.

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