Association of Serum Adiponectin Biomarker with Metabolic Syndrome Components in Koreans with Extremely High HDL Cholesterol Levels in General Health Checkup

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Abstract: Adiponectin and high-density lipoprotein cholesterol (HDL-C) are negative predictors for cardio-metabolic disorders. This study explored adiponectin’s role in predicting multiple metabolic syndrome components (multi-MetSC) in subjects with extremely high HDL-C levels overall and by sex. We enrolled adults with extremely high HDL-C levels (≥90 mg/dL) in general health checkups and compared adiponectin levels in subjects with and without multi-MetSC. Among 274 subjects (median 44 years, female 79.6%), 19 (6.9%) had a multi-MetSC. The adiponectin level was significantly lower in subjects with multi-MetSC than without (females: 9.2 [6.2–13.3] µg/mL, p = 0.039; males: 6.9 ± 2.4 vs. 10.0 ± 5.2 µg/mL, p = 0.013). The optimal cutoff values to predict multi-MetSC were 9.7 µg/mL (sensitivity 64%, specificity 74%) in females and 9.6 µg/mL (sensitivity 100%, specificity 44%) in males. Compared with the high adiponectin group, the low group revealed higher fasting glucose in females and higher waist circumference, visceral fat area, and HDL-C levels in males. Multiple logistic regression analysis confirmed adiponectin as an independent predictor of multi-MetSC (OR 0.85, 95% CI 0.71–0.97). Adiponectin could be a potential biomarker for multi-MetSC in general health checkup subjects with extremely high HDL-C levels. There were sex differences in the metabolic risk factors between low and high adiponectin groups.

Keywords: adiponectin; metabolic syndrome; biomarkers

1. Introduction
Metabolic syndrome (MetS) is a cluster of multi-dimensional cardiovascular risk factors that increase the chance of developing type 2 diabetes or cardiovascular diseases. The definition has been formulated from the 1999 World Health Organization, 2001 National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP-III), 2002 European Group for the study of insulin resistance, and 2009 International Diabetes Federation formulation [1–5]. The prevalence of MetS ranges from 15% to 35% in adults with various demographics and diagnostic criteria, being more common in men than in women (in Asians, a prevalence of 21% in men, 15% in women; in Koreans, 28% in men, 19% in women) [6–8]. The most widely used guideline is the NCEP ATP-III, which includes five components: (1) Abdominal obesity: waist circumference ≥102 cm (men) or ≥88 cm (women), or for Asian, ≥90 cm (men) or ≥80 cm (women); (2) blood pressure (BP) ≥130/85 mmHg or medicated; (3) fasting plasma glucose (FPG) ≥100 mg/dL or medicated; (4) high-density lipoprotein cholesterol (HDL-C) <40 mg/dL (men) or <50 mg/dL (women) or medicated; (5) triglycerides ≥150 mg/dL or medicated [2]. Considering the key features of the MetS are associated with insulin resistance, it may be valuable to explore some simple blood-based biomarkers emphasizing insulin resistance in a general health checkup package.
An adipocyte-derived cytokine, adiponectin could be a blood-based biomarker to reflect MetS components, with primary insulin sensitization, anti-inflammatory, and anti-atherogenic properties [9]. Epidemiological studies showed a positive correlation between adiponectin and HDL-C, suggesting both are negative predictors of MetS as well as atherosclerotic cardiovascular diseases [10–12], although their relationship has not been explored for extremely high HDL-C levels where there are paradoxical increases in cardiovascular or all-cause mortalities [13–16]. The diagnostic accuracy of adiponectin for MetS has been confirmed in a Korean population [17,18], but the adoption of this new supplementary blood test in routine health checkups has lacked sufficient evidence to prove additional benefits on top of the current blood tests, which include glucose, HDL-C, and triglycerides. Moreover, the usefulness of adiponectin as a metabolic risk predictor of low or normal HDL-C levels has been reported [17–19], but the usefulness of adiponectin in subjects with extremely high HDL-C levels has not been fully elucidated.

The purpose of this study is to explore the association of the serum adiponectin biomarker with multiple MetS components (multi-MetSC, ≥2 components) in subjects undergoing general health checkups with extremely high HDL-C levels, overall and by sex. In detail, we explored the correlation between serum adiponectin levels and parameters reflecting MetS components and tested whether serum adiponectin is an independent predictor for multi-MetSC among other general health checkup blood variables.

2. Materials and Methods

2.1. Study Design and Population

This was a retrospective cross-sectional study in a single tertiary medical center. Between April and September 2017, we included consecutive adults (age ≥ 19 years) with extremely high HDL-C (≥90 mg/dL) in a general health check-up program which includes body composition analysis and adiponectin measurement. We excluded subjects with a medical history of cardiovascular diseases. We retrospectively reviewed their medical records, including routine check-up results and self-administered questionnaires. In this study, multi-MetS was defined as the presence of any two of the following four components based on the NCEP ATP-III with Asian modification [2,7]: (1) Abdominal obesity: waist circumference ≥90 cm (men) or ≥80 cm (women); (2) BP ≥130/85 mmHg or medicated; (3) FPG ≥100 mg/dL or medicated; (4) triglycerides ≥150 mg/dL or medicated.

2.2. Anthropometric and Body Composition Measurements

All subjects underwent routine anthropometric measurements, including BP, body weight, height, and waist and hip circumferences. BMI (kg/m²) was calculated by dividing body weight (kg) by height squared (m²) [20]. Body composition was analyzed using InBody770 (InBody Co., Ltd., Seoul, Korea) based on the direct segmental multi-frequency bioelectrical impedance method [21], determining the parameters of body fat mass (kg), body fat (%), and visceral fat area (cm²).

2.3. Laboratory Analysis

After at least 12 h of overnight fasting, blood samples were drawn as the routine GME protocol and were centrifuged within one hour. The serum samples were stored at −80 °C until use. Total cholesterol, low-density lipoprotein cholesterol, HDL-C, and triglycerides were measured by enzymatic reagents (Kyowa Kirin Co., Ltd., Tokyo, Japan) on a chemistry analyzer (TBA-200FR NEO, Toshiba Medical System Co., Tokyo, Japan). Low-density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald formula: LDL-C = Total cholesterol-(triglycerides/5)-HDL-C. Serum adiponectin was measured by Randox immunoturbidimetric adiponectin assay (Randox Laboratories Ltd., Crumlin, UK), according to the manufacturer’s protocol [22].
2.4. Statistical Analysis

Data are expressed as frequency (percentage) for categorical variables or a mean ± standard deviation or median with the interquartile range for continuous variables. All continuous data were tested for normal distribution using Kolmogorov-Smirnov nonparametric tests. We performed comparison analysis in two groups with Chi-square or Fisher’s exact test (categorical variables) and an independent T-test or Mann–Whitney U test (continuous variables) in four groups with the Kruskal–Wallis test with Turkey’s post hoc test. We assessed the correlation between adiponectin levels and continuous variables using Pearson’s correlation coefficient (r). The correlation was interpreted as negligible (<0.1), weak (0.1–0.39), moderate (0.40–0.69), strong (0.70–0.89), or very strong (≥0.9) based on the absolute magnitude [23]. We analyzed the ROC curves for serum adiponectin levels to predict multi-MetSC. Finally, we performed the univariate binary and multiple logistic regression analysis of blood variables reflecting metabolic syndrome components or lipid profiles for predicting multi-MetSC (p-value threshold of 0.2 for multiple regression, likelihood method for CI). All the statistical analysis was performed by web-based analysis with R 4.2 (http://web-r.org, accessed on 5 June 2022). The level of significance (alpha) was set to 0.05 (two-tailed).

3. Results
3.1. Characteristics of the Study Population

Characteristics of the 274 subjects overall and by sex are presented in Table 1. The median age was 44 [37–51] years with females comprising 79.6%. The median body mass index (BMI) was 20.8 [19.3–22.6] kg/m²; triglycerides, 57.5 [45.0–75.0] mg/dL; and adiponectin, 11.6 [8.5–14.7] µg/mL. Females had significantly lower BP, FPS, liver enzymes, BMI, waist circumference, and visceral fat areas but a higher total and total percentage of body fat. The serum adiponectin level was significantly higher in females than in males (12.0 [9.4–15.6] vs. 8.6 [6.2–12.0] µg/mL, p < 0.001). Females revealed lower rates of MetS components (high BP, high FPS, and multi-MetSC) than males (p < 0.05).

Table 1. Characteristics of the study population.

|                      | All Subjects N = 274 | Females N = 218 | Males N = 56 | P   |
|----------------------|----------------------|-----------------|--------------|-----|
| Age, years           | 44.0 [37.0;51.0]     | 43.0 [36.0;48.0] | 49.0 [41.5;55.0] | <0.001 |
| Family history *     |                      |                 |              |     |
| Hypertension         | 111 (46.6%)          | 89 (46.6%)      | 22 (46.8%)   | 0.98 |
| Diabetes mellitus    | 60 (25.2%)           | 50 (26.2%)      | 10 (21.3%)   | 0.49 |
| Smoking †            |                      |                 |              |     |
| Never                | 196 (80.0%)          | 183 (95.8%)     | 13 (24.1%)   | <0.001 |
| Past smoker          | 29 (11.8%)           | 6 (3.1%)        | 23 (42.6%)   |     |
| Current smoker       | 20 (8.2%)            | 2 (1.0%)        | 18 (33.3%)   |     |
| Alcohol consumption ‡|                      |                 |              | <0.001 |
| None                 | 84 (31.3%)           | 81 (38.2%)      | 3 (5.4%)     |     |
| Adequate             | 137 (51.1%)          | 113 (53.3%)     | 24 (42.9%)   |     |
| Intermediate         | 39 (14.6%)           | 17 (8.0%)       | 22 (39.3%)   |     |
| Heavy alcohol use    | 8 (3.0%)             | 1 (0.5%)        | 7 (12.5%)    |     |
| Exercise frequency § |                      |                 |              | 0.095 |
| 0/week               | 98 (35.8%)           | 83 (38.1%)      | 15 (26.8%)   |     |
| 1–4/week             | 111 (40.5%)          | 89 (40.8%)      | 22 (39.3%)   |     |
| ≥5/week              | 65 (23.7%)           | 46 (21.1%)      | 19 (33.9%)   |     |
### Table 1. Cont.

|                      | All Subjects | Females   | Males    | \( p \)  |
|----------------------|--------------|-----------|----------|----------|
| **Anthropometric and body composition measurements** |              |           |          |          |
| Weight, kg           | 53.8 [49.9;61.0] | 52.8 [49.1;57.3] | 65.0 [57.8;71.4] | <0.001   |
| BMI, kg/m\(^2\)      | 20.8 [19.3;22.6] | 20.6 [19.2;22.1] | 22.1 [20.1;23.4] | 0.005    |
| WC, cm               | 72.0 [67.5;78.0] | 70.8 [67.0;75.0] | 78.2 [74.0;83.5] | <0.001   |
| Waist/hip ratio      | 0.82 [0.77;0.85] | 0.81 [0.76;0.84] | 0.89 [0.83;0.91] | <0.001   |
| Body fat mass, kg    | 13.9 [11.9;16.1] | 14.0 [12.2;16.9] | 12.4 [8.5;15.1] | <0.001   |
| Body fat, %          | 25.4 ± 6.1     | 27.1 ± 5.0   | 18.5 ± 5.1   | <0.001   |
| VFA, cm\(^2\)       | 52.0 [36.0;74.0] | 48.0 [34.0;66.0] | 85.0 [62.5;101.0] | <0.001   |
| Systolic BP, mmHg    | 116.0 [104.0;124.0] | 111.5 [102.0;120.0] | 125.0 [117.5;132.5] | <0.001   |
| Diastolic BP, mmHg   | 71.0 [63.0;79.0] | 69.0 [61.0;77.0] | 76.0 [68.5;80.5] | <0.001   |
| **Laboratory analysis** |              |           |          |          |
| Hemoglobin, mg/dL    | 13.5 [12.9;14.3] | 13.3 [12.6;13.8] | 15.1 [14.6;15.6] | <0.001   |
| FPG, mg/dL           | 89.0 [83.0;94.0] | 87.5 [82.0;93.0] | 93.0 [87.0;99.0] | <0.001   |
| HbA1c, %             | 5.3 [5.1;5.5]   | 5.3 [5.1;5.5] | 5.4 [5.2;5.5] | 0.36     |
| Total-C, mg/dL       | 214.0 [195.0;234.0] | 214.0 [196.0;234.0] | 215.5 [188.5;233.0] | 0.76     |
| LDL-C, mg/dL         | 105.0 [85.0;123.0] | 105.0 [85.0;121.0] | 104.5 [83.0;126.0] | 0.92     |
| HDL-C, mg/dL         | 95.0 [92.0;98.0] | 95.0 [92.0;98.0] | 95.0 [91.5;99.0] | 0.86     |
| Triglycerides, mg/dL | 57.5 [45.0;75.0] | 57.5 [44.0;75.0] | 57.5 [48.0;73.5] | 0.63     |
| AST, mg/dL           | 22.0 [19.0;26.0] | 21.0 [18.0;25.0] | 27.5 [23.0;37.0] | <0.001   |
| ALT, mg/dL           | 15.0 [12.0;21.0] | 15.0 [11.0;18.0] | 22.0 [16.5;32.0] | <0.001   |
| γGT, mg/dL           | 18.0 [13.0;27.0] | 16.0 [12.0;22.0] | 36.5 [23.5;60.0] | <0.001   |
| TB, mg/dL            | 0.8 [0.7;1.1]   | 0.8 [0.6;1.0] | 1.1 [1.0;1.4] | <0.001   |
| Creatinine, mg/dL    | 0.8 [0.7;0.9]   | 0.8 [0.7;0.8] | 1.0 [0.9;1.1] | <0.001   |
| GFR, mL/min/1.73 m\(^2\) | 84.0 [76.0;91.0] | 85.0 [77.0;91.0] | 80.5 [76.0;90.0] | 0.25     |
| Adiponectin, µg/mL   | 11.6 [8.5;14.7] | 12.0 [9.4;15.6] | 8.6 [6.2;12.0] | <0.001   |
| **Medications**      |              |           |          |          |
| Hypertension         | 10 (3.6%)     | 4 (1.8%) | 6 (10.7%) | 0.006    |
| Diabetes mellitus    | 4 (1.5%)      | 0 (0.0%) | 4 (7.1%) | 0.002    |
| Dyslipidemia         | 13 (4.7%)     | 8 (3.7%) | 5 (8.9%) | 0.15     |
| **Number of Metabolic syndrome components** |          |          |          |          |
| 0                    | 182 (66.4%)   | 160 (73.4%) | 22 (39.3%) | <0.001   |
| 1                    | 73 (26.8%)    | 47 (21.6%) | 26 (46.4%) | <0.001   |
| 2                    | 13 (4.7%)     | 7 (3.2%) | 6 (10.7%) | 0.018    |
| Abdominal obesity    | 30 (10.9%)    | 25 (11.5%) | 5 (8.9%) | 0.76     |
| High BP              | 56 (20.4%)    | 31 (14.2%) | 25 (44.6%) | <0.001   |
| High FPG             | 30 (10.9%)    | 16 (7.3%) | 14 (25.0%) | <0.001   |
| High triglycerides   | 1 (0.4%)      | 1 (0.5%) | 0 (0.0%) | 1.00     |
| 2                    | 13 (4.7%)     | 7 (3.2%) | 6 (10.7%) | 0.018    |
| Abd + BP             | 4 (1.5%)      | 2 (0.9%) | 2 (3.6%) | 0.19     |
Table 1. Cont.

|                      | All Subjects | Females | Males | $p$ |
|----------------------|--------------|---------|-------|-----|
|                      | $N = 274$    | $N = 218$ | $N = 56$ |     |
| Abd + FPG            | 2 (0.7%)     | 2 (0.9%) | 0 (0.0%) | 1.00 |
| BP + FPG             | 6 (2.1%)     | 2 (0.9%) | 4 (7.1%) | 0.017 |
| FPG + TG             | 1 (0.4%)     | 1 (0.5%) | 0 (0.0%) | 1.00 |
| 3 Abd + BP + FPG     | 6 (2.2%)     | 4 (1.8%) | 2 (3.6%) | 0.61 |

Values are expressed as median [interquartile range], mean ± standard deviation, or number (percentage). $p$ is based on the comparison between females and males using the Mann–Whitney U or independent t-test (quantitative variables) and Chi-square or Fisher’s exact test (categorical variables); bold figures indicate $p < 0.05$. * Data were available for 238 subjects (females, 191; males, 47). † Data were available for 268 subjects (females, 212; males, 56). Adequate is defined as one standard drink (14 g of ethanol, as found in five ounces of wine or 12 ounces of beer) per day or seven standard drinks per week with no more than three drinks per occasion. Heavy alcohol use is defined as binge drinking (four drinks for women and five drinks for men) on five or more days in the past month [24]. § One time means ≥30 min of moderate-intensity aerobic physical activity (3–5.9 MET, for example walking at moderate or brisk pace, slow cycling, gardening, golf, tennis, or ballroom dancing [25]. ¶ NCEP ATP-III with Asian modification: (1) Abdominal obesity: waist circumference ≥90 cm (men) or ≥80 cm (women); (2) BP ≥130/85 mmHg or medicated; (3) FPG ≥100 mg/dL or medicated; (4) HDL-C < 40 mg/dL (men) or <50 mg/dL (women) or medicated; (5) triglycerides ≥150 mg/dL or medicated. Abbreviations: BP, blood pressure; BMI, body mass index; WC, waist circumference; VFA, visceral fat area; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; Total-C, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; AST, aspartate transaminase; ALT, alanine transaminase; γGT, gamma-glutamyl transferase; TB, total bilirubin; GFR, glomerular filtration rate based on the Modification of Diet in Renal Disease Study equation; Abd, abdominal obesity.

Among the 218 females, 53 (24.3%) were postmenopausal. The serum adiponectin level was significantly higher in post- than in pre-menopausal females (14.0 [10.6–18.0] vs. 11.7 [9.1–14.6] µg/mL, $p = 0.005$) (Supplementary Materials Figure S1).

Hormone model assessment for insulin resistance (HOMA-IR) was available in 97 subjects (females, 80; males, 17), with a median value of 0.94 [0.68–1.29] and no significant difference between females and males (0.95 [0.66–1.25] vs. 0.85 [0.69–1.87], $p = 0.404$).

3.2. Correlations between Serum Adiponectin Levels and Parameters Reflecting MetS Components

The Pearson’s correlation coefficients between adiponectin levels and parameters reflecting MetS components or lipid profiles are shown in Table 2. In all subjects, serum adiponectin levels showed a weak negative correlation with BMI, waist circumference, waist-to-hip ratio, body fat mass, visceral fat area, FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; Total-C, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; AST, aspartate transaminase; ALT, alanine transaminase; γGT, gamma-glutamyl transferase; TB, total bilirubin; GFR, glomerular filtration rate based on the Modification of Diet in Renal Disease Study equation; Abd, abdominal obesity.

Table 2. Correlations between adiponectin levels and parameters reflecting MetS components or lipid profiles.

|                      | All Subjects | Females | Males | $p$ | $p$ | $p$ | $p$ |
|----------------------|--------------|---------|-------|-----|-----|-----|-----|
|                      | $N = 274$    | $N = 218$ | $N = 56$ |     |     |     |     |
| BMI, kg/m$^2$        | −0.255       | <0.0001 | −0.170 | 0.012 | −0.389 | 0.003 |
| WC, cm               | −0.307       | <0.0001 | −0.200 | 0.003 | −0.339 | 0.011 |
| Waist/hip ratio      | −0.247       | <0.0001 | −0.119 | 0.080 | −0.252 | 0.061 |
| Body fat mass, kg    | −0.129       | 0.032   | −0.140 | 0.039 | −0.373 | 0.005 |
| Body fat, %          | 0.029        | 0.629   | −0.094 | 0.167 | −0.358 | 0.007 |
| VFA, cm$^2$          | −0.217       | <0.0001 | −0.100 | 0.140 | −0.227 | 0.093 |
| Systolic BP, mmHg    | −0.102       | 0.093   | −0.008 | 0.907 | −0.096 | 0.612 |
| Diastolic BP, mmHg   | −0.113       | 0.063   | −0.034 | 0.620 | −0.136 | 0.319 |
| FPG, mg/dL           | −0.191       | 0.002   | −0.160 | 0.018 | −0.079 | 0.565 |
| HbA1c, %             | −0.006       | 0.916   | 0.017  | 0.806 | 0.063  | 0.647 |
### Table 2. Cont.

|                      | All Subjects | Females | Males |
|----------------------|--------------|---------|-------|
|                      | N = 274      | N = 218 | N = 56|
| **r**                | **p**        | **r**   | **p** |
| Total-C, mg/dL       | 0.062        | 0.310   | 0.073 | 0.286 | 0.021 | 0.877 |
| LDL-C, mg/dL         | 0.027        | 0.651   | 0.031 | 0.647 | 0.049 | 0.722 |
| HDL-C, mg/dL         | 0.041        | 0.496   | 0.061 | 0.370 | -0.100 | 0.464 |
| Triglycerides, mg/dL | -0.131       | **0.030** | -0.128 | 0.058 | -0.140 | 0.304 |

Pearson’s correlation coefficient (r). Bold figures indicate p < 0.05. Variables: see Table 1.

#### 3.3. Comparison of Serum Adiponectin Levels with or without Multi-MetSC

Of the 274 subjects, no MetS component was seen in 182 (66.4%), one component in 73 (26.6%), two components in 13 (4.7%), three components in 6 (2.2%), and four components in 0 (0.0%) (Table 1, Figure 1). Multi-MetSC (≥2 MetS components) was observed in 19 (6.9%) subjects, more frequent in males than in females (14.3% vs. 5.0%, p = 0.015). Adiponectin levels were significantly lower in subjects with multi-MetS than in those without (all subjects: 7.9 [5.9–9.6] vs. 11.8 [8.8–14.9] µg/mL, p = 0.001; females: 9.2 [6.2–13.3] vs. 12.0 [9.7–15.9] µg/mL, p = 0.039; males: 6.9 ± 2.4 vs. 10.0 ± 5.2 µg/mL, p = 0.013) (Figure 2).

#### 3.4. Optimal Cutoff Values of Adiponectin to Predict Multi-MetSC

The receiver-operating characteristic (ROC) curves demonstrated that serum adiponectin levels could predict multi-MetSC in all subjects and by sex, and the optimal cutoff values are shown in Figure 3. In all subjects, adiponectin showed an area under the curve (AUC) of 0.743 (p = 0.001) with a cutoff of ≤9.7 µg/mL, sensitivity of 79%, and specificity of 69%. In females, there was an AUC of 0.685 (p = 0.04) with a cutoff of ≤9.7 µg/mL; in males, an AUC of 0.680 (p = 0.03) with a cutoff of ≤9.6 µg/mL.

#### 3.5. Comparison of General Health Checkup Parameters between Low and High Adiponectin Groups

The characteristics of subjects with low and high adiponectin levels (according to the cutoff values in Figure 3) are presented in Table 3. The low group showed significantly higher body weight, BMI, waist circumference, waist-to-hip ratio, and visceral fat area than the high group both in all subjects and in males (p < 0.05), though not in females (p > 0.3). The low group revealed significantly higher FPG than the high group in all subjects and females (p < 0.05).

#### 3.6. Logistic Regression Analysis of Blood Variables including Adiponectin for Predicting Multi-MetSC

In univariate binary logistic regression analysis, adiponectin (odds ratio [OR] 0.81 with 95% confidence interval [CI] 0.70–0.91, p < 0.001), FPS (OR 1.16, 95% CI 1.10–1.24, p < 0.001), and HbA1c (OR 1.16, 95% CI 2.02–18.4, p = 0.002) were associated with multi-MetSC. Multiple logistic regression analysis confirmed adiponectin as a significant negative predictor for multi-MetSC (OR 0.85, 95% CI 0.69–0.96, p = 0.031) for all subjects (Table 4).
Of the 274 subjects, no MetS component was seen in 182 (66.4%), one component in 73 (26.6%), two components in 13 (4.7%), three components in 6 (2.2%), and four components in 0 (0.0%) (Table 1, Figure 1). Multi-MetSC (≥2 MetS components) was observed in 0 (0.0%) (all subjects: 7.9 [5.9–9.6] vs. 11.8 [8.8–14.9] µg/mL, p = 0.039; males: 6.9 ± 2.4 vs. 10.0 ± 5.2 µg/mL, p = 0.013) with a cutoff of 9.7 µg/mL, sensitivity of 79%, and specificity of 81%.)

Figure 1. Box-and-whisker dot plots. Four group comparisons of serum adiponectin levels according to the number of metabolic syndrome (MetS) components. Kruskal–Wallis test with Turkey’s post hoc test was used: (0 vs. 1) p = 0.99, (0 vs. 2) p = 0.04, (0 vs. 3) p = 0.11, (1 vs. 2) p = 0.075, (1 vs. 3) p = 0.15, and (2 vs. 3) p = 0.99.

The characteristics of subjects with low and high adiponectin levels (according to the cutoff values in Figure 3) are presented in Table 3. The low group showed significantly higher FPG than the high group in all subjects (all subjects: 9.7 [8.4–14.9] vs. 7.7 [6.1–9.6] mmol/L, p = 0.001; females: 9.2 [6.2–13.3] vs. 12.0 [8.5–21.2] mmol/L, p = 0.03). The low group revealed significantly higher body weight, BMI, waist circumference, waist-to-hip ratio, and visceral fat area than the high group both in all subjects and in males (all subjects: 83.3 ± 18.1 vs. 76.6 ± 12.5 kg, p = 0.001; males: 88.6 ± 14.6 vs. 78.1 ± 12.2 kg, p = 0.001) and females (all subjects: 79.6 ± 15.9 vs. 72.3 ± 12.7 kg, p = 0.001; females: 76.3 ± 12.6 vs. 68.2 ± 12.4 kg, p = 0.001).

An independent two-sample test (t-test or Mann–Whitney test) was used after the normality test. The receiver-operating characteristic (ROC) curves demonstrated that serum adiponectin levels could predict multi-MetSC in all subjects and by sex, and the optimal cutoff value by the Youden index is presented with sensitivity (Sens), specificity (Spec), positive predictive value (PPV), and negative predictive value (NPV).

Figure 2. Box-and-whisker dot plots. Two group comparisons of serum adiponectin levels with or without multiple metabolic syndrome components (≥2) in all subjects (a), females (b), and males (c). An independent two-sample test (t-test or Mann–Whitney test) was used after the normality test.

Figure 3. The receiver operating characteristic curves for serum adiponectin levels to predict multi-metabolic syndrome components (a): All subjects, (b): Females, and (c): Males. The area under the curve (AUC) with a 95% confidence interval is shown in each group. The optimal cutoff value by the Youden index is presented with sensitivity (Sens), specificity (Spec), positive predictive value (PPV), and negative predictive value (NPV).
Table 3. Comparison of general health checkup parameters between the low and high serum adiponectin level groups.

| Parameters                        | All Subjects | Females | Males | \( p \) Value |
|-----------------------------------|--------------|---------|-------|--------------|
| **Adiponectin, µg/mL**            | Low Group N = 95 | High Group N = 179 | Low Group N = 60 | High Group N = 158 | Low Group N = 35 | High Group N = 21 | \( p \) Value |
| Adiponectin, µg/mL                | 7.7 [5.8;8.6] | 13.7 [11.7;17.1] | <0.001 | 7.9 [5.8;8.8] | 13.8 [11.7;17.2] | <0.001 | 6.9 [5.5;8.1] | 13.5 [11.8;14.9] | <0.001 |
| Age, years                        | 45.0 [38.0;49.5] | 44.0 [37.0;51.0] | 0.75 | 43.0 [37.5;47.0] | 43.0 [36.0;50.0] | 0.67 | 47.5 ± 9.7 | 53.0 ± 14.2 | 0.09 |
| Anthropometric and body composition measurements |
| Body weight, kg                   | 57.1 [50.5;65.0] | 53.0 [49.8;57.8] | 0.003 | 52.9 [48.5;58.3] | 52.8 [49.4;57.2] | 0.98 | 68.3 ± 10.7 | 61.0 ± 6.4 | 0.002 |
| BMI, kg/m²                        | 21.2 [19.8;23.2] | 20.6 [19.1;22.1] | 0.014 | 20.6 [19.4;22.2] | 20.6 [19.1;22.1] | 0.68 | 22.9 [21.1;24.4] | 20.6 [19.3;22.3] | 0.002 |
| Waist/hip ratio                   | 0.83 ± 0.06 | 0.80 ± 0.06 | <0.001 | 0.81 [0.77;0.83] | 0.81 [0.75;0.84] | 0.49 | 0.89 ± 0.05 | 0.84 ± 0.06 | 0.008 |
| Body fat mass, kg                 | 13.9 [12.0;16.5] | 13.7 [11.8;16.0] | 0.50 | 13.9 [12.4;16.5] | 14.2 [12.2;16.9] | 1.00 | 13.9 [10.8;16.5] | 9.5 [8.1;12.5] | 0.001 |
| Body fat, %                       | 24.7 ± 5.8 | 25.7 ± 6.3 | 0.17 | 27.2 ± 4.6 | 27.1 ± 5.2 | 0.80 | 20.2 ± 5.0 | 15.7 ± 3.8 | 0.001 |
| VFA, cm²                          | 59.0 [43.0;91.5] | 50.0 [33.0;68.0] | 0.005 | 48.0 [38.0;65.0] | 48.0 [32.0;66.0] | 0.70 | 89.0 ± 29.7 | 71.1 ± 26.7 | 0.028 |
| Laboratory analysis               |              |         |       |              |               |       |              |               |       |
| Hemoglobin, mg/dL                 | 14.1 [13.1;14.9] | 13.4 [12.8;14.0] | <0.001 | 13.6 [12.6;14.1] | 13.2 [12.6;13.8] | 0.08 | 15.2 ± 1.1 | 14.9 ± 0.9 | 0.32 |
| HbA1c, %                          | 5.3 [5.1;5.5] | 5.3 [5.2;5.5] | 0.79 | 5.3 [5.1;5.5] | 5.3 [5.2;5.5] | 0.97 | 5.3 [5.2;5.5] | 5.4 [5.3;5.6] | 0.30 |
| Total-C, mg/dL                    | 212.0 [191.5;233.0] | 214.0 [196.5;235.5] | 0.37 | 212.3 ± 26.6 | 218.1 ± 27.6 | 0.17 | 217.8 ± 32.2 | 212.5 ± 30.9 | 0.55 |
| LDL-C, mg/dL                      | 104.0 [83.5;124.0] | 105.0 [86.5;121.0] | 0.47 | 103.1 ± 25.7 | 107.4 ± 25.9 | 0.28 | 105.0 [82.0;128.0] | 101.0 [89.0;119.0] | 0.87 |
| AST, mg/dL                        | 22.0 [19.0;28.5] | 22.0 [19.0;26.0] | 0.31 | 20.0 [18.0;23.0] | 21.0 [18.0;25.0] | 0.18 | 28.0 [23.5;37.5] | 26.0 [23.0;31.0] | 0.38 |
| ALT, mg/dL                        | 15.0 [12.0;24.5] | 15.0 [12.0;20.0] | 0.13 | 14.0 [11.0;18.0] | 15.0 [11.0;18.0] | 0.64 | 22.0 [15.5;32.5] | 22.0 [19.0;25.0] | 0.75 |
| γGT, mg/dL                        | 22.0 [14.0;41.5] | 16.0 [13.0;24.0] | <0.001 | 17.0 [12.5;23.5] | 16.0 [12.0;21.0] | 0.51 | 46.0 [26.0;63.5] | 27.0 [21.0;37.0] | 0.028 |
| TB, mg/dL                         | 0.9 [0.7;1.2] | 0.8 [0.6;1.0] | 0.009 | 0.8 [0.6;1.0] | 0.8 [0.6;1.0] | 0.97 | 1.1 [1.0;1.4] | 1.1 [0.8;1.3] | 0.44 |
| Creatinine, mg/dL                 | 0.8 [0.7;0.9] | 0.8 [0.7;0.8] | 0.025 | 0.7 [0.7;0.8] | 0.8 [0.7;0.8] | 0.14 | 1.0 ± 0.1 | 1.0 ± 0.1 | 0.56 |
| GFR, mL/min/1.73 m²               | 86.0 [78.0;91.0] | 84.0 [76.0;91.0] | 0.14 | 87.5 [79.5;91.0] | 84.0 [76.0;91.0] | 0.039 | 81.0 [76.5;89.5] | 79.0 [76.0;90.0] | 0.77 |
| Metabolites components reflecting variables | All Subjects | Females | Males |
|-------------------------------------------|-------------|---------|-------|
| **WC, cm** | 74.5 [68.5;80.2] | 71.0 [67.0;75.0] | **<0.001** |
| **Systolic BP, mmHg** | 120.0 [108.0;128.0] | 113.0 [102.0;120.0] | **0.007** |
| **Diastolic BP, mmHg** | 72.0 [65.0;79.0] | 69.0 [61.0;79.0] | 0.08 |
| **FPG, mg/dL** | 93.0 [86.5;96.5] | 87.0 [82.0;91.5] | **<0.001** |
| **HDL-C, mg/dL** | 95.0 [93.0;99.0] | 94.0 [92.0;98.0] | 0.13 |
| **Triglycerides, mg/dL** | 61.0 [48.0;79.0] | 56.0 [43.0;73.0] | **0.054** |

**Metabolic syndrome components**

| Abdominal obesity | 12 (12.6%) | 18 (10.1%) | 0.66 |
| High BP | 26 (27.4%) | 30 (16.8%) | 0.055 |
| High FPG | 18 (18.9%) | 12 (6.7%) | **0.004** |
| High triglycerides | 1 (1.1%) | 0 (0.0%) | 0.35 |
| ≥2 components | 15 (15.8%) | 4 (2.2%) | **<0.001** |
| ≥3 components | 4 (4.2%) | 2 (1.1%) | 0.19 |

Values are expressed as median [interquartile range], mean ± standard deviation, or number (percentage). Mann–Whitney U or independent t-test (quantitative variables) and Chi-square or Fisher’s exact test (categorical variables) were used; bold figures indicate *p* < 0.05. The low (≤9.7 μg/mL) and high (>9.7 μg/mL) adiponectin level groups in total subjects and females; the low (≤9.6 μg/mL) and high (>9.6 μg/mL) in males. Abbreviations: see Table 1.
Table 4. Logistic regression analysis of blood variables reflecting metabolic syndrome components or lipid profiles for predicting multi-MetSC in subjects with extremely high HDL-C levels.

|                     | All Subjects |                     | Females |                     | Males |                     |
|---------------------|--------------|---------------------|---------|---------------------|-------|---------------------|
|                     | Univariate   | Multivariable       | Univariate | Multivariable       | Univariate | Multivariable |
|                     | OR (95% CI)  | p                   | OR (95% CI)  | p                   | OR (95% CI)  | p                   |
| Adiponectin         | 0.81 (0.70–0.91) | <0.001               | 0.85 (0.71–0.97) | **0.031**           | 0.82 (0.69–0.96) | **0.019**           | 0.85 (0.70–1.00) | 0.065               | 0.83 (0.64–1.01) | 0.103               | 0.71 (0.39–1.01) | 0.144               |
| FPG                 | 1.16 (1.10–1.24) | <0.001               | 1.20 (1.11–1.31) | <0.001              | 1.24 (1.13–1.39) | **<0.001**          | 1.24 (1.12–1.41) | **<0.001**          | 1.10 (1.04–1.20) | **0.006**           | 1.29 (1.07–1.74) | 0.031               |
| HbA1c               | 5.62 (2.02–18.4) | **0.002**              | 0.26 (0.04–1.66) | 0.161               | 6.50 (0.85–50.6) | 0.069               | 1.14 (0.10–13.4) | 0.917               | 3.87 (1.24–16.9) | **0.037**           | 0.03 (0.00–1.58) | 0.131               |
| Total-C             | 1.02 (1.00–1.03) | 0.065               | 1.03 (0.96–1.10) | 0.329               | 1.01 (0.99–1.04) | 0.244               | 1.02 (0.99–1.04) | 0.152               | 1.03 (0.99–1.07) | 0.126               |
| LDL-C               | 1.01 (1.00–1.03) | 0.098               | 0.98 (0.92–1.06) | 0.597               | 1.01 (0.99–1.04) | 0.293               | 1.02 (0.99–1.05) | 0.226               |
| HDL-C               | 0.98 (0.88–1.06) | 0.626               | 0.97 (0.84–1.07) | 0.659               | 0.99 (0.82–1.16) | 0.882               |
| Triglycerides       | 1.01 (1.00–1.03) | 0.090               | 1.01 (0.99–1.03) | 0.380               | 1.01 (0.99–1.03) | 0.284               | 1.02 (0.99–1.05) | 0.190               | 1.01 (0.97–1.05) | 0.636               |

Bold figures indicate \( p < 0.05 \). OR, odds ratio; CI, confidence interval. Variables: see Table 1.
4. Discussion

In this extremely high HDL-C level cohort, subjects with multi-MetSC showed significantly lower serum adiponectin levels than those without, in all subjects and by sex. The association of adiponectin levels and MetS components has been reported as a global systematic review or meta-analysis [26,27] and as a Korean study by sex [28]. For the Korean reference values, two large-scale studies were reported. Park et al. reported adiponectin references as 13.4 [9.3–18.9] µg/mL in females and 8.2 [6.2–11.0] µg/mL in males via the enzyme-linked immunosorbent assay (ELISA) method with a Korean health checkup cohort [29]. Koh et al. reported adiponectin references as 12.82 [9.58–16.70] µg/mL in females and 8.90 [6.24–12.74] µg/mL in males via radioimmunoassay [28]. As a cross-sectional study, low adiponectin’s association with MetS has been reported in apparently healthy subjects (MetS vs. no MetS: females 5.7 ± 1.8 vs. 8.6 ± 2.1 µg/mL, p < 0.001; males 3.3 ± 1.8 vs. 4.4 ± 2.1 µg/mL, p = 0.002) by ELISA [18], in non-diabetic adults (MetS vs. no MetS: females 10.12 [7.62–13.41] vs. 11.74 [8.80–15.22] µg/mL, p < 0.001; males 6.00 [4.32–8.53] vs. 8.00 [5.62–11.33] µg/mL, p < 0.001) by radioimmunoassay [28], and in farmers (MetS vs. no MetS: females 7.8 ± 3.2 vs. 9.6 ± 3.8 µg/mL; males 5.1 ± 2.1 vs. 7.6 ± 3.2 µg/mL, all p < 0.05) by ELISA [30]. As a prospective study, the baseline adiponectin levels predicted de-novo MetS after a median 2.4-year follow-up (MetS vs. no MetS: females 11.0 [7.8–14.8] vs. 12.2 [9.1–15.5] µg/mL, p < 0.001; males 7.1 [4.9–9.5] vs. 8.6 [6.3–11.7] µg/mL, p < 0.001) by radioimmunoassay [17].

Our study is unique in terms of the study subjects, including Koreans with extremely high HDL-C levels (≥90 mg/dL) in general health checkups. Koh et al. studied non-diabetic Koreans, reporting baseline HDL-C levels as 47.4 ± 11.0 mg/dL in females and 46.2 ± 11.7 mg/dL in males, which are low to normal [28]. Compared to several Korean studies with low to normal HDL-C levels in healthy volunteers, our baseline adiponectin levels measured by immunoturbidimetric assay are higher than some studies using ELISA [18,30,31] but similar to the two large-scale studies (one by ELISA, the other, radioimmunoassay) [28,29]. Although almost all of the previous studies reported a positive relationship between adiponectin and HDL-C levels [12,19,29,30,32], our study showed no significant correlation between the two in all subjects. Furthermore, in males, the low adiponectin group with a higher rate of multi-MetSC revealed paradoxically higher HDL-C levels than the high group (96.7 ± 4.9 vs. 94.0 ± 3.0 mg/dL, p = 0.014), suggesting that low adiponectin levels could predict metabolic risk even in subjects with extremely high HDL-C levels. For females, we should consider using a level of 130 mg/dL as the “extremely high” threshold since the cardiovascular risk level at 130 is similar to that of 90 in males in a Korean population [16]. Unfortunately, with our study subjects, the median value of adiponectin levels was 94.7 [92.0–98.0] µg/mL with a range of 90–133 µg/mL in females, which may not fully represent the true extremely high HDL-C levels (≥130 mg/dL). For the mechanism related to adiponectin and HDL-C, a specific single nucleotide polymorphism has been reported [33] but the metabolic association between the two is considered to be regulated by a complex genetic pathway and environmental factors [34]. The positive correlation between adiponectin and HDL-C levels has been explained by adiponectin-induced up-regulation of HDL-C: adiponectin increases HDL-C via hepatic production of apo-A1 and ATP-binding cassette transporter A1 [35] or via activation of lipoprotein lipase [36]. However, in this study, the mechanism regarding the paradoxical relationship between adiponectin and HDL-C levels in males with extremely high HDL-C levels is not clear. We only speculate that heavy alcohol intake may have played a role. Subjects with extremely high HDL-C levels tend to show heavy alcohol drinking, which may be related to lower serum adiponectin levels in Korean men [16,37]. Therefore, considering the mutual effects between adiponectin and HDL-C during the metabolic risk evaluation is reasonable, especially in subjects with extremely high HDL-C levels.

In this study, the optimal cutoff value to predict multi-MetSC was 9.7 µg/mL (sensitivity 79%, specificity 69%) for all subjects, 9.7 µg/mL (sensitivity 64%, specificity 74%) in females, and 9.6 µg/mL (sensitivity 100%, specificity 44%) in males. The relatively high
sensitivity seems good for health screening purposes. Similar to the previous studies, our study demonstrated the independent association of low adiponectin levels with multi-MetSC in all subjects (OR 0.85, 95% CI 0.71–0.97, p = 0.031). By sex, there was a trend but not enough statistical significance (females: OR 0.85, 95% CI 0.70–1.00, p = 0.065; males: OR 0.71, 95% CI 0.39–1.01, p = 0.14) in multiple logistic regression with blood variables reflecting MetS components or lipid profiles, which may be due to the low number of study subjects. Pathophysiological roles of adiponectin for multi-MetSC have been suggested. Mendelian randomization studies were inconsistent for the causality, one supporting an adiponectin causal relationship to insulin sensitivity [38], another not supporting causation of insulin resistance or type 2 diabetes [39]. The Adipo Q gene, from which human adiponectin is encoded, is located on chromosomes 3 and 17, which is well-established for influence on phenotypes of MetS [40]. The adiponectin level’s inverse relationship with the presence of MetS is considered to be mediated by insulin sensitivity, anti-inflammatory, and anti-atherosclerotic effects [9,38].

Here, we presented sex-specific characteristics of the low vs. high adiponectin groups in subjects with extremely high HDL-C levels, which were not presented in previous studies. In males, the low adiponectin group had a significantly higher waist circumference and visceral fat area, as we expected. In females, however, the expected obese phenotype was not distinguishable, but elevated FPG was significant in the low adiponectin group compared with the high adiponectin group. Sex differences in the progression of metabolic risk factors have been emphasized in diabetes development [41], and sex-specific biomarker levels should be considered in future studies [16].

This study has several limitations. First, it was a small cross-sectional study. Second, some inquiries about family history, lifestyle, and nutritional habits are missing data. Third, female subgroup analysis by the status of menopause was limited (Supplementary Materials), with a lack of information about long-term hormone replacement therapy or oral contraceptives containing different progestogens. There have been complex reports regarding the influence of adiponectin levels on menopausal status, hormone replacement therapy, or contraception [42–44]. Fourth, the target outcome was multi-MetSC (≥ two components out of four) instead of the more robust MetS (≥ three components out of five) or major adverse cardiovascular events. Even though the MetS components may be easy to assess in a clinical setting, it would be important to learn if the adiponectin level can help to determine the atherosclerotic risk for subjects with extremely high HDL-C. Therefore, in the future, a larger prospective study with solid outcomes (atherosclerotic cardiovascular diseases or all-cause or cardiovascular mortality) analyzing HDL-subclasses [45] might be useful to assess adiponectin’s role as a biomarker for metabolic or atherosclerotic cardiovascular diseases.

5. Conclusions

Adiponectin showed the potential to be an incremental blood-based biomarker for multi-MetSC in subjects with extremely high HDL-C levels in general medical check-ups. Sex differences were noted in the metabolic risk factors between the low and high adiponectin groups.

Supplementary Materials: The following supporting information can be downloaded at https://www.mdpi.com/article/10.3390/metabo12111086/s1, Figure S1: Comparison of serum adiponectin levels between pre- and post-menopausal females; Figure S2: Comparisons of serum adiponectin levels with or without multiple metabolic syndrome components in pre-menopausal females and post-menopausal females; Figure S3: The receiver operating characteristic curves for serum adiponectin levels to predict multi-metabolic syndrome components; Table S1: Logistic regression analysis of blood variables reflecting metabolic syndrome components or lipid profiles for predicting multi-MetSC in pre-menopausal females with extremely high HDL-C levels.
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Informed Consent Statement: Patient consent was waived as the research required no additional intervention and involved no more than minimal risk to subjects.

Data Availability Statement: All the data described in this study are available within the article or its supplementary materials.

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