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Evaluation of adropin level and insulin resistance in non-alcoholic fatty liver patients: a meta-analysis of studies

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Abstract. – OBJECTIVE: The recently discovered protein adropin is a highly conserved polypeptide that plays critical functions in energy homeostasis, metabolic processes, fat metabolism, and insulin resistance. On the other hand, non-alcoholic fatty liver disease (NAFLD) is a medical condition that causes the buildup of fat in the liver cells in individuals who consume little or no alcohol. The frequency of NAFLD is rising globally, and it is frequently linked to obesity, insulin resistance, type 2 diabetes, and metabolic syndrome. Therefore, this study evaluates the association between adropin levels and insulin resistance in individuals with and without NAFLD.

MATERIALS AND METHODS: Data from Scopus, Science Direct, and PubMed were searched between January 1, 2012, and February 18, 2024, using precise terms and stated criteria. Comprehensive Meta-Analysis V. 2 (Biostat, Englewood, NJ, USA) was used for data analysis, and Random-effect models were used to estimate the pooled mean differences with 95% CIs of adropin level, insulin level, and homeostatic model assessment for insulin resistance (HOMA-IR) associated with the exposures of interest.

RESULTS: Our results revealed that adropin blood levels are significantly reduced in NAFLD patients compared to control individuals. The mean difference in adropin blood levels was 2.391 ng/ml with a 95% CI of 1.127 to 3.656 with I^2 99.6. on the other hand, insulin resistance was significantly higher in NAFLD compared to controls (MD: -1.668, 95% CI: -2.333 to -1.002, I^2=86%).

CONCLUSIONS: Our findings reveal that adropin levels are significantly greater in healthy controls than in NAFLD patients, suggesting that adropin may have a preventative effect on NAFLD. This meta-analysis highlights how closely adropin and insulin resistance interact in non-alcoholic fatty liver disease. Also, it may open the door to new diagnostic tools and therapeutic modalities.

Key Words:
Adropin, Insulin resistance, NAFLD, Fatty liver, Meta-analysis.

Introduction

Non-alcoholic fatty liver disease (NAFLD) is a medical condition characterized by the accumulation of fat in the liver cells of individuals who consume little to no alcohol. There is a spectrum of liver conditions, from simple fatty liver (steatosis) to non-alcoholic steatohepatitis (NASH), which causes inflammation and damage to liver cells[1,2]. The prevalence of NAFLD is increasing worldwide, and it is often associated with obesity, insulin resistance, type 2 diabetes, and metabolic syndrome[3,4]. Several factors contribute to the development of NAFLD, including genetics, environment, and lifestyle[5-7]. NAFLD is often asymptomatic in its early stages. However, it can progress to more severe conditions, such as necrotizing sclerosing hepatitis (NASH), fibrosis, and cirrhosis (liver cancer)[8].

The peptide hormone adropin has been investigated for its potential role in metabolic regulation, including its potential association with NAFLD[9]. The *ENHO* gene encodes adropin, and it is expressed in various tissues, including the liver, brain, and skeletal muscle[10]. Adropin has been as-

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sociated with NAFLD. In addition to regulating energy homeostasis and insulin sensitivity, adropin has also been implicated in regulating lipid metabolism and energy homeostasis[11]. According to studies[12], the expression of adropin in the liver may play a role in the development and progression of NAFLD in patients. Furthermore, adropin may protect against NAFLD-related liver damage and inflammation. While these studies suggest a potential association between adropin and NAFLD, the exact mechanisms and clinical implications are still under investigation. To fully understand adropin's role in NAFLD and whether it can be used as a therapeutic target, more research is needed.

Materials and Methods

Data Search

Three databases (PubMed, Science Direct, and Scopus) were searched between January 1, 2012, and Feb 18, 2024. The following combined keywords were used for searching the databases: "NAFLD"; "NAFLD and adropin"; "fatty liver, and adropin"; "metabolic syndrome, and adropin". Furthermore, all relevant studies' lists of references were manually checked to identify further studies. The meta-analysis was reported following the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement[13].

Study Selection

The selection of studies was restricted to adult human subjects and English-language articles. This analysis does not include case reports, review papers, or editorials. Studies that offered sufficient information on NAFLD and adropin were chosen. Excluded studies included insufficient information about the total number of cases.

Data Abstraction

Using a standardized form, data were extracted from each study that met the inclusion criteria. The following data were extracted: the surname of the first author, the design of the study, sex ratio, sample size, age, country, and data relevant to comorbid chronic disease. Moreover, means and standard deviations (SD) for adropin level, insulin level, homeostatic model assessment for insulin resistance (HOMA-IR), and body mass index (BMI) in both cases and control, *p*-value for comparisons between cases and controls for outcome of interest, method of adropin level measurement, adropin level, insulin level, HOMA-IR measurements. Two investigators (FA and RA) extracted the relevant data.

Quality Assessment

To evaluate the possibility of bias, we utilized the Joanna Briggs Institute (JBI) critical appraisal checklist for case series[14]. The JBI addresses ten items concerning selection, confounding, and information bias to assess the case series' internal validity. For each of the JBI checklist's items, there are four possible responses: "yes," "no," "unclear," or "not applicable". The JBI tool's usage was further described by Munn et al[14] in 2020. Usually, the results of the quality assessment of the included studies should not be shortened and reported as a score as was recommended previously[14]. The quality assessment of the included studies in this meta-analysis was carried out by SA.

Quantitative Data Synthesis and Analysis

Comprehensive Meta-Analysis V2 (Biostat, Englewood, NJ, USA) was used for data analysis. Statistical significance was attained when the *p*-value was lower than 0.05.

We calculated the mean differences (MDs) and their 95% confidence interval (CIs) for each continuous outcome. Random-effect models were used to estimate the pooled MDs with 95% CIs of adropin level, insulin level, and HOMA-IR associated with the exposures of interest. A random-effects model was used to incorporate heterogeneity among studies[15]. Heterogeneity in any analysis was tested using the I^2 statistic ($p<0.1$), which estimates the variation in study results explained by between-study heterogeneity rather than sampling error. Usually, an I^2 value >50% indicates considerable heterogeneity[15]. Egger's test was used to evaluate the presence of publication bias.

Results

Search Results and Study Characteristics

A total of 69 articles were identified from the 3 databases examined and other sources. After excluding duplicated or overlapping articles and removing reviews and editorials, 42 articles met the primary search criteria. Six studies that reported the level of adropin, insulin level, and HOMA-IR were included in the meta-analysis (Figure 1).

Quantitative Analysis

This meta-analysis involving six studies (one on children and five on adults) revealed that adropin

blood levels are higher in controls compared to cases with NAFLD (p-value lower than 0.05) (Figure 2). The mean difference in adropin blood levels was 2.391 ng/ml with a 95% CI of 1.127 to 3.656 with I^2 99.6. Heterogeneity was high among studies with an I-squared value of 99 (Figure 2). Although no significant difference in insulin levels was detected between control and NAFLD cases (MD: -25.775, 95% CI: -39.493 to 91.034, I^2 99.9 (Figure 3), insulin resistance was significantly higher in NAFLD compared to controls (MD: -1.668, 95% CI: -2.333 to -1.002, I^2=86%) (Figure 4). This meta-analysis highlights a clear distinction in adropin levels between controls and NAFLD patients, with elevated adropin levels observed in controls. Although insulin levels did not show a significant difference, insulin resistance was notably higher in NAFLD patients. The high heterogeneity in adropin and insulin level data suggests variability in the studies included, which should be considered when interpreting these results.

Quality Assessment

Table II shows the results of the quality assessment using the JBI critical appraisal checklist. Except for one study, all studies had clear inclusion criteria and consecutively recruited the participants. However, no study complete inclusion of participants. All included studies measured the outcomes of interest using a standardized, reliable method for all cases and controls and identified the cases using a valid method. All studies clearly reported the demographics of the participants, the clinical information of the participants, and the follow-up results. Four out of the six studies clearly presented the results by site(s)/clinic(s) demographic information.

Discussion

The present meta-analysis introduces interesting findings regarding the association between adropin levels, insulin levels, and insulin resistance in individuals with and without NAFLD. The analysis of six research reveals that adropin levels are significantly higher in controls than in NAFLD patients, as shown in Figure 2, leading to a potential protective role of adropin against NAFLD. This outcome is consistent with numerous investigations that have shown adropin to be involved in lipid metabolism and energy regulation[16,18,21]. Adult NAFLD patients showed lower serum adropin levels, according to Kutlu et al[16] observations. Additionally, they discovered reduced serum adropin levels in insulin-resistant individuals, which is consistent with our findings and those of other researchers in the literature.

The groups did not show any significant differences in insulin levels; however, the NAFLD cases showed a significant rise in insulin resistance. This finding aligns clearly with the pathogenesis of NAFLD, where insulin resistance is a major factor, as reported by many previous studies[22-24]. Adropin was repeatedly demonstrated to be essential for preserving glucose homeostasis, boost-

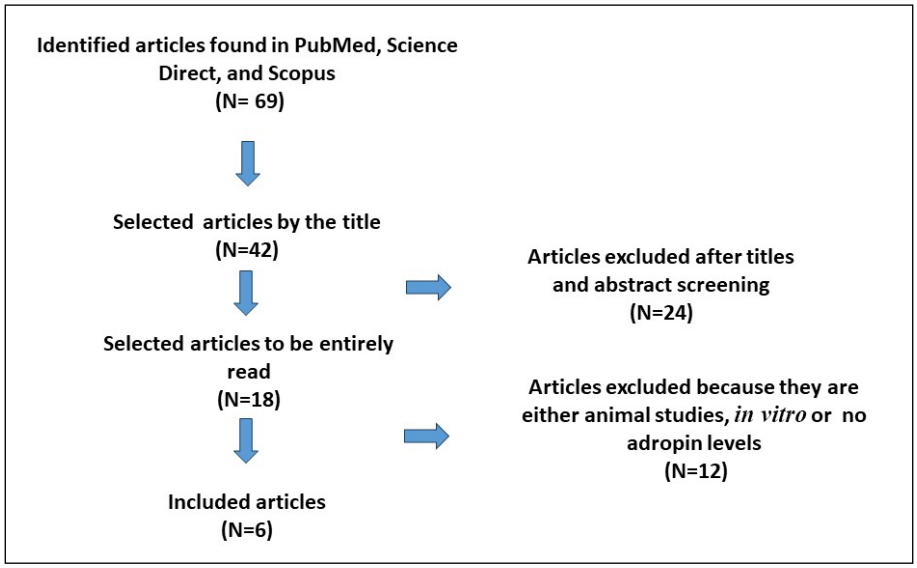

Figure 1. Flow chart of the literature search and study selection.

Table I. Characteristics of included studies.

First author (publication year)	Country/ study design	Sample size (case/ control)	Sex (male/female)		Age (mean±SD) year		BMI (mean±SD) kg/m²		Adropin level (mean±SD) ng/ml		*p*-value	Insulin (µIU/ml)		HOMA-IR		*p*-value
			Case	Control	Case	Control	Case	Control	Case	Control		Case	Control	Case	Control	
Sayın et al[12] (2014)	Turkey/ case-control	100 (64/36)	37/27	19/17	Obese with NAFLD 12.9±2.1 Obese without NAFLD 13.05±2.4	2.0±13.2	27.89±6.97	20.09±5.08	Obese with NAFLD 2.9±0.5 Obese without NAFLD 3.5±1.2	9.2±1.2	0.001	Obese with NAFLD 15.6±5.7 Obese without NAFLD 162.5±41.8	104.9±8.3	Obese with NAFLD 3.1±0.9 Obese without NAFLD 3.6±0.7	1.3±0.5	0.000
Kutlu et al[16] (2019)	Turkey/ case-control	81 (51/30)	26/25	14/16	9.96±37.9	9.5±34.8	29.2±5.2	27.8±4.9	0.588±0.261	0.894±0.301	<0.001	17.1±12.3	9.3±6.1	4.1±2.8	1.60±0.78	<0.001
Chen et al[17] (2020)	China/ case-control	109 (47/62)	NAFL 14/12 NASH 9/12	B-ultrasound control 23/24 Histological control 9/6	NA	NA	NAFL 23.10±4.46 NASH 23.12±5.18	B-ultrasound control 22.64±3.63 Histological control 21.64±3.21	NAFL 17.82±6.90 NASH 9.99±5.51	B-ultrasound Control 22.70±6.32 Histological Control 21.93±6.63	<0.05	NAFL 10.92±4.40 NAFL 10.92±4.40	B-ultrasound control 6.71±1.51 Histological control 6.37±2.41	NAFL 2.54±1.12 NASH 2.50±0.95	B-ultrasound control 1.45±0.39 Histological control 1.29±0.45	NA
Li et al[18] (2021)	China/ case-control	62 (30/32)	10/20	11/21	35.1±9.5	35.1±4.8	36.88±5.79	21.46±1.61	2.02±2.92	5.52±0.65	<0.001	15.89	5.5	4.28	1.27	0.02
Zaki et al[19] (2022)	Egypt/ case-control	80 (40/40)	0/40	0/40	33.5±3.4	32.7±2.6	33.65±4.047	32.59±3.56	0.110±0.013	0.165±0.019	0.001	Not measured	Not measured	Not measured	Not measured	NA
Zhang et al[20] (2023)	China/ case-control	44 (22/22)	17/5	17/5	38.55±9.33	40.18±10.64	31.0	22.75	2.79±0.47	3.27±0.79	<0.05	15.25	5.95	6.23	1.25	NA

BMI: body mass index; HOMA-IR: homeostatic model assessment for insulin resistance; NAFLD: non-alcoholic fatty liver disease; NASH: non-alcoholic steatohepatitis.

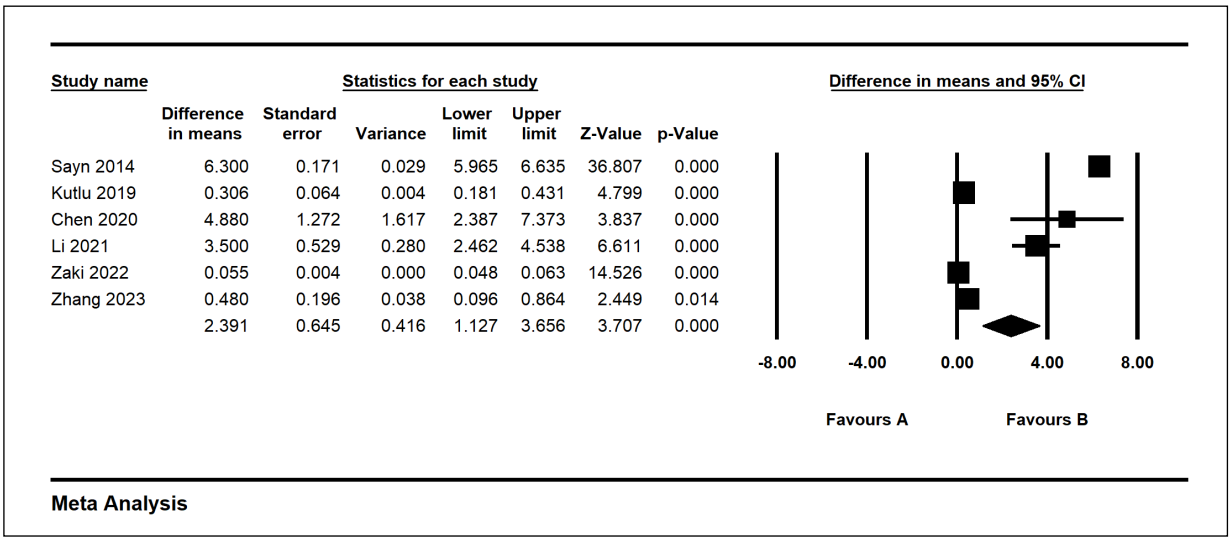

Figure 2. Forest plot of meta-analysis of studies evaluating adropin levels in control participants compared to NAFLD cases.

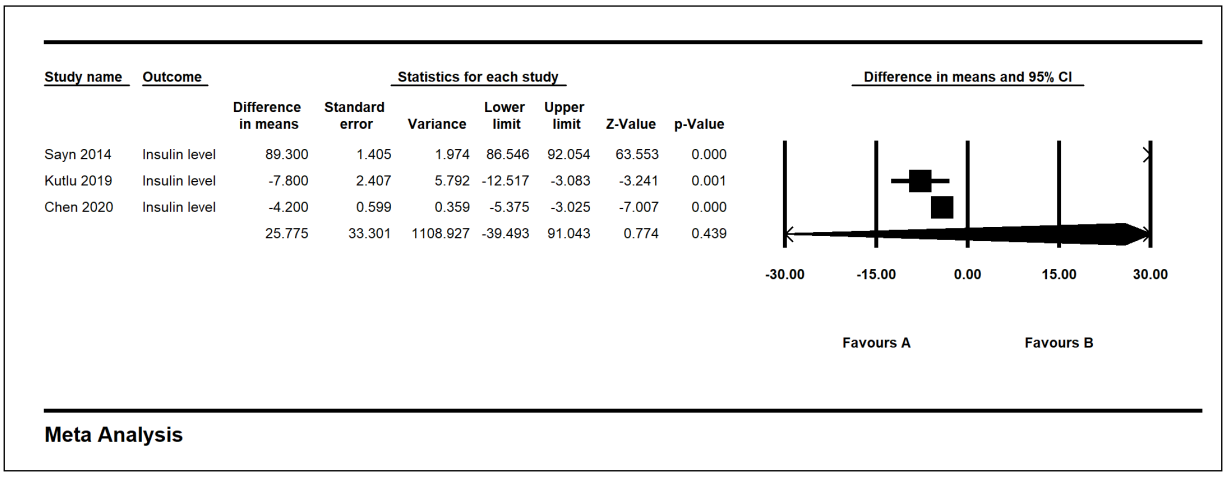

Figure 3. Forest plot of meta-analysis of studies evaluating insulin levels in control participants compared to NAFLD cases.

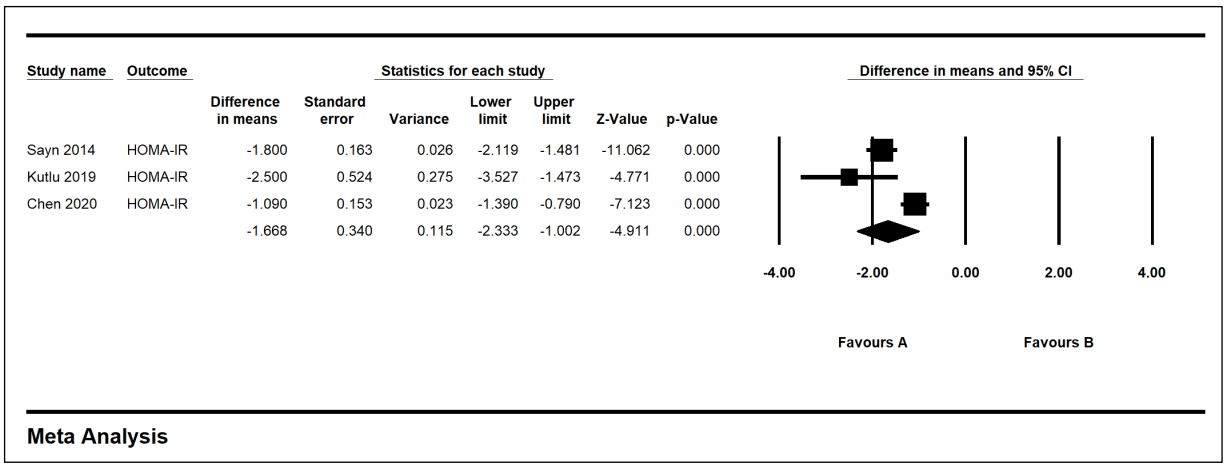

Figure 4. Forest plot of meta-analysis of studies evaluating insulin resistance (HOMA-IR) in control participants compared to NAFLD cases.

Table II. The results of the quality assessment using the Joanna Briggs Institute JBI critical appraisal checklist.

Study	Zhang et al[20] 2023	Zaki et al[19] (2022)	Li et al[18] (2021)	Chen et al[17] (2020)	Kutlu et al[16] (2019)	Sayın et al[12] (2014)
Were there clear criteria for inclusion in the case series?	Yes	No	Yes	Yes	Yes	Yes
Was the condition measured in a standard, reliable way for all participants included in the case series?	Yes	Yes	Yes	Yes	Yes	Yes
Were valid methods used for identification of the condition for all participants included in the case series?	Yes	Yes	Yes	Yes	Yes	Yes
Did the case series have consecutive inclusion of participants?	Yes	No	Yes	Yes	Yes	No
Did the case series have complete inclusion of participants?	No	No	No	No	No	No
Was there clear reporting of the demographics of the participants in the study?	Yes	Yes	Yes	Yes	Yes	Yes
Was there clear reporting of clinical information of the participants?	Yes	Yes	Yes	Yes	Yes	Yes
Were the outcomes or follow up results of cases clearly reported?	Yes	Yes	Yes	Yes	Yes	Yes
Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	No	No	Yes	Yes	Yes	Yes
Was statistical analysis appropriate?	Yes	Yes	Yes	Yes	Yes	Yes

Egger's test revealed no significant publication bias (Egger's test: p=0.08994).

ing glucose utilization, enhancing glucose tolerance, and lowering insulin resistance in earlier research[10,25,26]. On the other hand, long-term high-fat/high-sucrose diet consumption decreased liver adropin expression and may be linked to dysregulated glucose metabolism and hepatic insulin resistance[27]. Various mechanisms are proposed to clarify the function of adropin in disorders linked with the metabolic syndrome. Synthetic adropin was found to increase the hepatocyte cultures' total lipoprotein lipase (LPL) synthesis and secretion in experimental research. Because it catalyzes the hydrolysis of endogenous and exogenous triacylglycerol complexes into glycerol and free fatty acids, LPL, which is found at the capillary endothelium, is crucial for the removal of triacylglycerol-rich plasma lipoproteins. Thus, it is proposed that LPL protects against NAFLD and that adropin increases the production of this protective factor[28,29].

Endothelial dysfunction has been linked to NAFLD[30]. Interestingly, Baka et al[30] found that severe intrauterine fetal growth limitation was associated with higher maternal levels of adropin. This finding suggests that adropin serves as a regulatory feedback mechanism to counteract endothelial placental malfunction. Nitric oxide generation primarily controls endothelial activities, which are also crucial for insulin sensitivity and metabolic regulation[31]. It has been demonstrated that adropin stimulates the production of endothelial nitric oxide synthetase, and adropin deficiency has been linked to lower nitric oxide levels in endothelial cells[32,33].

These results highlight how closely adropin and insulin resistance interact in non-alcoholic fatty liver disease. They also emphasize the necessity for more investigation into the therapeutic potential of adropin and the development of insulin resistance-targeting tactics in order to successfully manage non-alcoholic fatty liver disease (NAFLD). Furthermore, knowing how adropin functions in the context of NAFLD may open the door to new diagnostic tools and therapeutic modalities. This meta-analysis contributes to the

increasing amount of research showing the close relationship between metabolic variables and the onset and course of NAFLD.

Conclusions

In conclusion, our results show that adropin levels are much higher in healthy controls than in NAFLD patients, indicating that adropin may have a preventive effect against NAFLD. To understand the mechanisms by which adropin influences metabolic processes and to create focused interventions that may enhance outcomes for people with non-alcoholic fatty liver disease (NAFLD), more study is necessary. Adropin is highlighted as a promising option for upcoming diagnostic and treatment approaches by this meta-analysis, which adds to the increasing body of research connecting metabolic factors with non-alcoholic fatty liver disease (NAFLD).

Conflict of Interest
All authors declare no conflict of interest.

Informed Consent
Informed consent is not required since this study does not recruit human or animal subjects.

Ethics Approval
This is not required since this study does not recruit human or animal subjects.

AI Disclosure
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