**A thesis submitted to**

**Symbiosis Institute of Health sciences**

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***ASSOCIATION OF ADIPOQ/ADIPONECTIN AND POLYMORPHISMS ON INSULIN SENSITIVITY IN ANOREXIA NERVOSA PATIENTS***

For the partial fulfillment of the degree of Master of Science (M.Sc.) In Nutrition and Dietetics

By

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**Certificate**

This is to certify that the research work reported in the thesis entitled” Association of ADIPOQ/Adiponectin and Polymorphisms on Insulin Sensitivity in Anorexia Nervosa”, submitted to Symbiosis Institute of Health Sciences , Symbiosis International (Deemed University), Pune, has been carried out under my guidance.

Research Supervisor Research Co- Supervisor

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Date: Date:

Place: Place:

**Declaration**

I hereby declare that I have worked on project entitled “Association of ADIPOQ/Adiponectin and Polymorphisms on Insulin Sensitivity in Anorexia Nervosa”. The data mentioned in the thesis has been obtained after genuine work. Data obtained from other sources has been duly acknowledged. The results embodied in this thesis have not been submitted to any other university for any other degree.



Date: 28-5-24

Place: Pune Anushka Banerjee

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List of Abbreviations

|  |  |
| --- | --- |
| Abbreviations | Meaning |
| Apn | Adiponectin |
| AN | Anorexia Nervosa |
| HOMA IR | Homeostatic model assessment of Insulin resistance |
| ELISA | Enzyme-linked immunosorbent assay |
| PRISMA | Preferred reporting Items for Systematic Reviews and Meta-Analyses |

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**ABSTRACT**

**Background:** Anorexia Nervosa (AN) is a multifaceted mental health condition marked by severe malnourishment as a result of severe weight loss, excessive anxiety of gaining weight, and chronic dietary restriction. With regard to the connection between increased adiponectin secretion and improved insulin sensitivity in AN, there is a significant knowledge vacuum that this study attempts to fill. With an emphasis on the genetic variants +45T>G and +276G>T, the systematic review will investigate the relationship between insulin sensitivity in AN patients and the concentrations of adiponectin (ApN) and the ADIPOQ gene polymorphisms (which encode adipose-inducible protein kinase).

**Objectives:**

1. To study the association of ADIPOQ/ Adiponectin with increased insulin sensitivity in Anorexia Nervosa patients.
2. To identify polymorphisms in ADIPOQ gene and their association to impaired insulin sensitivity in Anorexia Nervosa patients.

**Methodology**: Studies examining the connection between insulin sensitivity and ADIPOQ gene variants in AN patients will be included in the systematic review. To find pertinent studies, a thorough search of the literature will be done across several databases. The inclusion criteria include cross-sectional studies that assess the levels of ApN (adiponectin) and HOMA-IR (Homeostatic Model Assessment of Insulin Resistance) in patients with AN. Two reviewers will independently extract data and evaluate its quality; a third reviewer will settle any conflicts. Should adequate homogeneity be identified among the studies, a meta-analysis will be carried out.

**Discussion:** This study comprehensively analyzes the complex metabolic dynamics in Anorexia Nervosa (AN) patients, emphasizing the associations between Adiponectin levels, ADIPOQ gene polymorphisms, and insulin sensitivity, while highlighting the necessity of personalized treatment strategies for effective management of metabolic health in AN.

**Conclusion:** The study indicates a complex relationship between elevated Adiponectin levels, improved insulin sensitivity, and ADIPOQ polymorphisms (+45 T>G and +276 G>T) in AN patients, necessitating further research to fully understand these metabolic interactions.

**Keywords:** "Anorexia Nervosa" AND "Adiponectin" AND "Insulin Sensitivity”; "ADIPOQ POLYMORPHISM" AND "Insulin Sensitivity"

**INTRODUCTION:**

Anorexia Nervosa (AN) stands as a complex psychiatric disorder of global concern, characterized by persistent dietary restriction, an intense fear of weight gain, distorted body image, and significant weight loss, often leading to severe malnutrition. This disorder poses substantial health risks worldwide, affecting physical and psychological well-being. A myriad of factors contributes to AN, encompassing genetic predispositions, traumatic experiences, environmental and cultural influences, peer pressure, and emotional well-being.The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) classifies AN based on criteria such as restriction of energy intake leading to significantly low body weight, intense fear of weight gain, and disturbed body weight perception or self-worth influenced by body weight. It further categorizes AN into restricting type, where binge-eating or purging is absent, and binge-eating/purging type, where such behaviors occur regularly.

Adiponectin, a pivotal protein in metabolic regulation, emerges as a noteworthy player in the context of anorexia nervosa. With its intricate involvement in energy homeostasis, glucose metabolism, and lipid balance, adiponectin holds a critical position in the broader understanding of the disorder. This protein, characterized by its structural resemblance to collagen VIII, collagen X, complement C1q, and TNF, is primarily synthesized by adipocytes and subsequently secreted into the bloodstream. While existing research highlights the decrease in plasma adiponectin levels in obesity and insulin resistance, intriguingly, anorexia nervosa reveals a distinct pattern. Studies indicate an association between anorexia nervosa and elevated levels of adiponectin (Housova et al, 2005; Dostálová et al. 2006,) This anomalous elevation is significant as it contradicts the typical trend seen in obesity-associated conditions. The underlying mechanisms behind this phenomenon are multifaceted. The lack of negative feedback exerted by fat mass on adiponectin production could contribute to its increased secretion.

Individuals with anorexia nervosa exhibit heightened insulin sensitivity, a phenomenon driven by the drastic reduction in body fat (Monteleone et al., 2008). This heightened sensitivity is primarily attributed to the depletion of fat tissue, particularly visceral fat, which produces inflammatory molecules that can interfere with insulin signalling (Golden et al, 2008).

Delving deeper into the molecular underpinnings, the ADIPOQ gene, encoding adiponectin, emerges as a focal point of investigation. This gene, mapped to the 3q27.3 region and comprising four exons, exhibits high expression in mature adipocytes, predominantly in white adipose tissue. Notably, it also shows expression in the paraventricular nucleus of the hypothalamus, a region associated with the regulation of hunger and satiety. Of particular interest are the +45T>G and +276G>T polymorphisms. A study by Karolina Natalia Ziora-Jakutowicz et al.,2021 shows that a significant association was found between loci ADIPOQ c.45, ADIPOQ , c. 276 in AN girls and Insulin sensitivity.

This research aims to address a critical knowledge gap concerning the precise relationship between heightened adiponectin secretion and enhanced insulin sensitivity in AN. The systematic review will meticulously scrutinize the association of the ADIPOQ gene (encoding adiponectin) and adiponectin concentrations with elevated insulin sensitivity specifically in individuals diagnosed with AN. Delving into molecular aspects, the ADIPOQ gene, located at the 3q27.3 region and highly expressed in mature adipocytes, emerges as a focal point. This gene's multifaceted role encompasses regulation of energy homeostasis, insulin sensitization, antiapoptotic activity, and modulation of atherosclerosis and inflammation.

To achieve this, healthy control subjects will be utilized to compare and contrast the results obtained from AN individual in terms of insulin sensitivity and adiponectin. Genetic polymorphisms within ADIPOQ, notably +45T>G and +276G>T, will be investigated for their impact, insulin sensitivity, and metabolic outcomes, providing valuable insights into AN's metabolic complexities.

This investigation into the relationship between heightened adiponectin secretion and enhanced insulin sensitivity in AN is crucial for developing targeted therapeutic interventions and effective management strategies. By bridging this existing knowledge gap, this research will contribute significantly to understanding and addressing the metabolic challenges associated with AN on a global scale, potentially leading to improved clinical outcomes and enhanced quality of life for affected individuals.

**OBJECTIVES**

1. **To study the association of ADIPOQ/ Adiponectin with increased insulin sensitivity in Anorexia Nervosa patients.**
2. **To identify polymorphisms in** **ADIPOQ gene and their association to impaired insulin sensitivity in Anorexia Nervosa patients.**

**MATERIALS AND METHODS**

The research question was defined based on the PICOST (Population, Intervention, Comparison, Outcomes, and Study design) format, focusing on non-pregnant individuals (adolescents, women, men) with or without anorexia nervosa, investigating the ADIPOQ gene/Adiponectin intervention's impact on insulin sensitivity through observational studies (cross-sectional, case-control, and longitudinal studies) from 2003 to 2023, while excluding pregnant individuals, animal studies, genetic markers other than ADIPOQ/Adiponectin, studies not reporting effects on insulin sensitivity, and research designs such as RCTs, quasi-experimental designs, opinion articles, scoping reviews, editorials, and any articles beyond the specified timeline.. The review protocol was developed according to PRISMA 2020 (Preferred reporting items for systematic review and meta-analysis protocols) statement. The methodology for the systematic review (SR) followed the guidelines and standards of PRISMA-2020 for reporting.

A. Search Strategy

In December 2023, a meticulously planned and executed systematic literature search was conducted using the reference management software Zotero. The aim was to identify all relevant studies, both published and unpublished, to minimize potential bias. A search-term-harvesting table was utilized to identify key search terms yielding the highest number of results. This table aided in refining the search strategy by combining Medical Subject Headings (MeSH) and other relevant terms for comprehensive coverage.

The search spanned five major databases renowned for global research coverage: PubMed, Web of Science, Science Direct, SCOPUS, and EBSCO. The search timeframe was limited to studies published between 2003 and 2023 to ensure relevance and currency.

B. Selection Criteria

The retrieved articles from the five databases were uploaded to **COVIDENCE 2.0 systematic review software (Veritas Health Innovation, Melbourne, Australia )** for the purpose of screening. . The criteria for selection of articles were based on the PICOST elements. The studies were from all continents of the world and limited to those published in English. All studies focussing on the outcome of insulin sensitivity in the context of Anorexia Nervosa with patients with Anorexia nervosa, Diabetes or MS as participants were considered for inclusion in the review .

The selected articles were processed through an organized methodology leveraging Covidence platforms for screening and inclusion purposes. Initially, the articles underwent a dual-phase screening process. During the first phase, the title and abstract of each article were independently reviewed by two reviewers, one being the author and the other a designated reviewer, against the pre-defined eligibility criteria. Upon this preliminary assessment, articles meeting the criteria proceeded to the second phase, where the full text was meticulously examined by the same reviewers independently for final verification before potential inclusion in the review. In instances where disagreements arose regarding the eligibility of studies, a third reviewer was consulted for resolution. Notably, reviews, systematic reviews, editorials, letters, and comments were systematically excluded. Articles meeting the stringent eligibility criteria were then formally selected for inclusion in the review, with excluded studies being clearly annotated with reasons within the Covidence platform. Additionally, for streamlined organization and retrieval, selected articles from PubMed were uploaded in PubMed format files, while articles from other databases (EBSCO, Web of Science, Scopus, ScienceDirect) were uploaded in .ris format onto the covidence app. The Covidence platform employed a robust duplicate removal mechanism to ensure the integrity of the dataset by identifying and eliminating any duplicate articles that overlapped among the five databases utilized in this study. This scientific approach minimizes redundancy and enhances the reliability of the data analysis, thus maintaining the quality and accuracy of the research outcomes.

C. Data Extraction and Quality Assessment

Data Extraction Process: Data extraction in this systematic review was conducted using a predefined Excel sheet specifically designed for this purpose. Cross-verification procedures were employed to detect and rectify any potential errors. The extracted information encompassed various dimensions including study details (such as author, publication year, and country of origin), participant characteristics (e.g., sample size, gender distribution), methodological aspects (domains measured, assessment tools utilized), study design, and the specific phenomenon or context under investigation. Furthermore, outcomes of interest were meticulously recorded, focusing on primary and secondary outcomes such as impacts on insulin sensitivity (e.g., HOMA IR), levels of ADIPOQ/ADIPONECTIN, and ADIPOQ polymorphisms.

Quality Assessment: To enhance the robustness and credibility of this review, the quality assessment of the included studies was performed using the JBI Critical Appraisal Checklist for Systematic Reviews and Research Synthesis developed by Moola et al. (2020). This comprehensive checklist allowed for a thorough evaluation of methodological rigor, potential biases, and overall reliability of the included studies, thus ensuring a high standard of evidence synthesis.

D. Strategy for Data Synthesis

Given the observed heterogeneity among the included studies, a quantitative synthesis approach was deemed inappropriate. Instead, a narrative synthesis methodology was adopted to systematically summarize and integrate the findings from individual studies. This narrative synthesis was guided by the distinctive characteristics of the studied populations and the specific outcomes of interest. For instance, emphasis was placed on elucidating the association of ADIPOQ/Adiponectin with enhanced insulin sensitivity in patients with Anorexia Nervosa, as well as exploring the role of ADIPOQ gene and its potential contribution to impaired insulin sensitivity in this patient population. This approach facilitated a comprehensive and nuanced understanding of the research landscape, allowing for meaningful interpretations and implications for clinical practice and future research endeavors.

E. Risk of Bias Assessment

The risk of bias in the selected studies was evaluated using the JBI Critical Appraisal Checklist for Systematic Reviews and Research Synthesis by Moola et al. (2020). This checklist encompasses various domains such as study design, participant selection, data collection methods, and statistical analysis, allowing for a comprehensive assessment of each study's methodological quality.

The assessment involved analysing potential biases that could affect the validity and reliability of the study findings. For instance, bias related to participant selection criteria, blinding of participants and researchers, completeness of outcome data, and overall study design were carefully examined.

Each domain was evaluated based on predefined criteria, and studies were categorized as having low, moderate, or high risk of bias accordingly. The assessment was conducted independently by two reviewers to ensure reliability and minimize subjective biases.

Studies with a high risk of bias were not excluded from the review but were considered in the interpretation of the findings and in discussing the overall quality of evidence. Transparency regarding the risk of bias assessment and its impact on the review's conclusions was maintained throughout the review process, enhancing the credibility and robustness of the research outcomes.

**RESULTS**

A total of thirty-five articles were retrieved during the literature search. After removing the duplicates, 24 articles were considered for screening using the eligibility criteria, Initial evaluation of articles through title and abstract resulted in only 19 articles meeting the selection criteria. During the full text evaluation, four articles were removed, (three of them because of wrong setting, one because of wrong patient population). Fifteen articles were finally selected for quality assessment. PRISMA diagram of the selection of studies is shown in Figure 1.

The study design comprises of 12 cross sectional studies (majority), two case control and one cohort study. However, all use standard tools (RIA kits, DNA extraction kits, ELISA) to collect data. Therefore, to assess the quality of selected studies, JBI Critical Appraisal Checklist for Systematic Reviews and Research Synthesis developed by Moola et al. (2020). was selected as the best, ‘applicable to all’ tool in this review, The quality of the studies was determined by the extent to which the items on above checklist were met by each of the articles. There were 8 checklist items in the tool which were all considered to be applicable in this review.

Studies from databases/registers **(n = 35)**

PubMed (n = 11)

Ebsco (n = 10)

Scopus (n = 7)

Web of Science (n = 6)

Science direct (n = 1)

**Identification**

Studies included in review **(n = 16)**

Studies excluded **(n = 5)**

Studies not retrieved **(n = 0)**

Studies assessed for eligibility **(n = 19)**

Studies sought for retrieval **(n = 19)**

Studies screened **(n = 24)**

Studies excluded **(n = 3)**

Wrong setting (n = 2)

Wrong patient population (n = 1)

References removed **(n = 10)**

Duplicates identified manually (n = 1)

Duplicates identified by Covidence (n = 9)

Marked as ineligible by automation tools (n = 0)

Other reasons (n = )

**Screening**

**Included**

**FIGURE 1: PRISMA FLOWCHART**

**TABLE 1: TABLE OF CHARECTERERESTICS**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| S. No. | Author and year | Location | Population, sample size | Type of study | Domain Measured | Tool Used | JBI tool Score |
| 1 | Sánchez et al., 2022 | Zulia state, Venezuela. | At position +45- T/T (n=30), T/G+G/G (n=5) | Case control study | Polymorphisms and HOMA IR | DNA-Salting out extraction technique and ELISA for Insulin levels | 6/8  (High) |
| 2 | Karolina Natalia Ziora-Jakutowicz et al., 2021 | Warsaw, Poland | 308 AN patients and 164 Healthy controls | Cross sectional Study | Polymorphisms and HOMA IR in AN (Connecting study) | Genomic Mini Ax Blood Spin kit | 6/8  (High) |
| 3 | Song et al., 2018 | Korea | 134 GG carriers, 167 T allele carriers | Cohort Study | Polymorphisms and HOMA IR | RIA kits, DNA isolation kit | 7/8  (High) |
| 4 | Prakash et al., 2015 | Uttar Pradesh, India | (+45T>G and +276G>T)- X/X (n=158) TG/X (186) TG/TG (298) | Case control study | Polymorphisms and HOMA IR | Salting out, ELISA | 5/8  (Moderate) |
| 5 | Kim et al., 2010 | Seoul, Korea | 276 G>T , n= 112 | Cross sectional study | Polymorphisms and HOMA IR | Genomic DNA purification kit and RIA kit | 7/8  (High) |
| 6 | Melistas et al., 2009 | Athens, Greece | +45: TT (249), TG (87), GG (7) +276: GG (172), GT (136), TT (27) | Cross sectional Study | Polymorphisms and HOMA IR | RIA kit and Taq man assays | 7/8  (High) |
| 7 | N Zhang et al., 2008 | Yantai, China | SNP +45-120 (T/T: 57, T/G: 54, G/G: 9) SNP+276 (G/G: 56, G/T: 46, T/T: 18) | Cross sectional study | Polymorphisms and HOMA IR | chemiluminescent methods and ELISA kit | 6/8  (High) |
| 8 | Křížová et al., 2008 | Prague, Czech Republic | 28 AN women vs 38 healthy controls | Cross sectional study | HOMA IR and ApN levels in AN patients | ELISA and RIA kits | 6/8  (High) |
| 9 | R. Dolezalova et al., 2007 | Prague, Czech Republic | 12 AN vs 18 Healthy Controls | Cross sectional study | HOMA IR and ApN levels in AN patients. | RIA kits | 6/8  (High) |
| 10 | Misra et al., 2007 | Boston, Massachusetts and Canada | 7 AN patient and 19 controls (age, 12–18 yr) | Cross sectional study | HOMA IR and ApN levels in AN patients | RIA kits | 8/8  (High) |
| 11 | Shin et al., 2006 | Seoul, korea | 45T>G: TT (n=161), G allele carriers (n=133) 276G>T: GG (n=145), T allele carriers (n=149) | Cross sectional study | Polymorphisms and HOMA IR | Genomic DNA purification kit and RIA kit | 5/8  (Morderate) |
| 12 | Dostálová I et al., 2006 | Prague, Czech Republic | 10 AN women vs 12 healthy controls | Cross sectional study | HOMA IR and ApN levels in AN patients | RIA kits | 7/8  (High) |
| 13 | Housova et al., 2005 | Prague, Czech Republic | 16 AN patients and 12 Healthy controls | Cross sectional study | HOMA IR and ApN levels in AN patients. | RIA kits | 6/8  (High) |
| 14 | Tagami et al., 2004 | Kyoto, Japan | 31 AN women vs 16 healthy controls | Cross sectional study | HOMA IR and ApN levels in AN patients. | RIA kit | 7/8  (High) |
| 15 | Misra et al.,2004 | Cambridge, Massachusetts | 23 AN women vs 21 healthy controls | Cross sectional study | HOMA IR and ApN levels in AN patient. | RIA kits | 7/8  (High) |

(HOMA IR – Homeostatic Model of Insulin Resistance- Measures Insulin Resistance; AN – Anorexia Nervosa; ApN- Adiponectin; RIA kits – Radioimmuno assay; +45T>G and +276G>T- Single Nucleotide Polymorphisms in Anorexia)

**TABLE 2: CATEGORISATION OF FINDINGS OF THE STUDIES**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **HOMA IR**  Present | | | Absent |
|  | Good | Mediocre | Poor |  |
| **Adiponectin in AN patient** | Dostálová I et al. (2006) | Tagami et al, 2004 |  | Misra et al, 2004(just has low IR) |
|  | Housova et al, 2005 |  | Křížová et al. 2008 (doesn’t mention, has data) |
|  | R. Dolezalova et al, 2007 |  | Misra et al., 2007 |
|  |  |  |  |  |
| **Association of +45 allele** | Melistas et al, 2009 | Prakash et al, 2015 | Shin et al, 2006 | N Zhang et al, 2008 |
|  | Karolina Natalia Ziora-Jakutowicz et al.,2021 | Sánchez et al., 2022 |  |  |
|  |  |  |  |  |
| **Association + 276 allele** | Shin et al, 2006 | N Zhang et al , 2008 | Kim et al, 2010 | Song et al , 2018 |
|  | Karolina Natalia Ziora-Jakutowicz et al.,2021 | Prakash et al, 2015 |  |  |
|  | Melistas et al, 2009 |  |  |  |

**TABLE 3: DATA FOR ASSOCIATION OF HOMA IR WITH ADIPONECTIN IN AN PATIENTS**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| S. No. | Author | No. of subjects (n) | | BMI (kg/m2) | | Adiponectin(µg/ml) | | Insulin sensitivity (%S by HOMA -IR) | |  | Association of HOMA IR with Adiponectin |
|  | P value |  |
|  |  | AN | Control | AN | Control | AN | Control | AN | Control |  |  |
| 1 | Křížová et al 2008 | 28 | 38 | 15.72±0.36 | 22.32±0.40 | 58.44±7.17 | 33.24±4.41 | 2.00 ± 0.18 | 2.97 ± 0.45 | <0.001 | Nil |
| 2 | R. Dolezalova et al. 2007 | 12 | 18 | 16·37 ± 0·41 | 22·96 ± 0·67 | 38·23 ± 5·32 | 24·94 ± 2·92 | 2·00 ± 0·18 | 2·97 ± 0·45 | <0.0001 | Positive Association was found between altered adiponectin in AN patients and alterations in metabolic changes including insulin sensitivity. |
| 3 | Misra et al. 2007 | 17 | 19 | 16.7 | 21.8 +/- 3.4 | 13.3 ±6.1 | 11.9 +/- 7.8 | 1.34 ± 0.56 | 14.2 +/-4.3 | <0.0001 | Nil |
| 4 | Dostálová et al. 2006 | 10 | 12 | 15.4 | 20.9 ± 0.7 | 46.4 ± 5.0 | 28.0 ± 2.9 | 0.36 ± 0.1 | 0.89 ± 0.1 | < 0.05 | Significant positive association between hyperadiponectinemia in patients with AN and increased IS |
| 5 | Housova et al, 2005 | 16 | 12 | 14.56 ± 0.43 | 22.47 ± 0.93 | 50.90 ± 5.45 | 26.01 ± 2.46 | 3.28 ±0.31 | 4.57 ± 0.4 | <0.05 | Positive association was found between altered adiponectin levels and reduced glucose concentrations. |
| 6 | Tagami et al.2004 | 31 | 16 | 14.0 ± 2.5 | 20.3 ± 1.5 | 11.0 ± 7.8 | 18.3 ± 9.8 | 1.0 ± 1.2 | 2.0 ± 1.0 | < 0.05 | Positive association was found between adiponectin, other cytokines and IR |
| 7 | Misra et al. 2004 | 23 | 21 | 16.7 ± 0.2 | 21.7 ± 0.8 | 0.0128±0.0011 | 0.0125 ± 0.0017 | 1.36 ± 0.14 | 3.08 ± 0.20 | <0.0001 | Nil |

(AN – Anorexia nervosa; HOMA -IR – Homeostatic Model of Insulin Resistance; p value – p Value for HOMA -IR)

**TABLE 4: DATA FOR ASSOCIATION OF POLYMORPHISM + 45 T>G AND HOMA IR**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| S. No. | Author | T/T | T/G | G/G | Control | P value | Association / Result |
| 1 | Sánchez et al., 2022 | 3.10 (0.90) | 4.40 (1.25) (T/T+ G/G) | 4.40 (1.25) (T/T+ G/G) | 1.3 (0.40) | <0.001 | A positive Association was found between SNP 45 T>G and development of MS ad DM2. |
| 2 | Karolina Natalia Ziora-Jakutowicz et al.,2021 | NA | NA | NA | NA | NA | Significant positive association was found between loci ADIPOQ c.45, ADIPOQ |
| 3 | Prakash et al., 2015 | NA | NA | NA | NA | NA | Significant positive association between Haplotype AMP1 (276 G>T., 45 T>G) and Insulin sensitivity |
| 4 | Melistas et al., 2009 | 2.12±1.23 | 1.86±0.99 (T/T+ G/G) | 1.86±0.99 (T/T+ G/G) | NA | NA | Significant positive association was found between SNP 45 T>G , SNP 276 G>T and development of IR |
| 5 | N Zhang et al., 2008 | 1.75 ± 1.18 | 1.88 ±1.29 | 2.13±1.32 | 1.42 ± 1.07 | 0.06 | Nil |
| 6 | Shin et al., 2006 | 2.02 ±0.16 | 1.96 ± 0.11  (T/T+ G/G) | 1.96 ±0.11  (T/T+ G/G) | 2.45±0.17  (T/T)  2.02 ±0.16  (T/T+G/G) | <0.05  <0.001 | Significant association was found between SNP 45 T>G and decreases in HOMA IR |

(SNP 45 T>G – Single nucleotide polymorphism of 45 allele present in Anorexia nervosa affecting Insulin sensitivity; MS – Metabolic Syndrome; DM2- Diabetic mellitus; AMP1- The Arabidopsis AMP1 gene; ADIPOQ gene- Adiponectin gene; IR- Insulin Resistance; HOMA -IR – Homeostatic Model of Insulin Resistance; p value – p Value for HOMA -IR)

|  |  |  |
| --- | --- | --- |
| **TABLE 5: DATA FOR ASSOCIATION OF POLYMORPHISM + 276 G>T AND HOMA IR** |  |  |

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| S No. | Author | G/G | G/T | T/T | Control | P value | Association /Result |
| 1 | Karolina Natalia Ziora-Jakutowicz et al., 2021 | NA | NA | NA | NA | NA | Significant positive association was found between loci ADIPOQ c.45, ADIPOQ |
| 2 | Song et al., 2018 | 0.18 | does not show effect | does not show effect | 1.74±0.04 | NA | Nil |
| 3 | Prakash et al., 2015 | NA | NA | NA | NA | NA | Significant positive association between Haplotype AMP1 (276 G>T. , 45 T>G) and Insulin sensitivity |
| 4 | Kim et al., 2010 | 2.03 ± 1.10 | 2.10 ±1.08 | 1.72 ± 0.85 | NA | NA | Positive Association was found between 276 G>T and HOMA IR |
| 5 | Melistas et al., 2009 | 1.90±1.00 | 2.25±1.34 | 2.25±1.34 | NA | NA | Significant positive association was found between polymorphisms 276 G>T, 45 T>G and HOMA IR |
| 6 | N Zhang et al., 2008 | 1.93 ±1.38 | 1.98 ±1.20 | 1.25 ± 0.53 | 1.42 ± 1.07 | 0.06 | Significant positive association was found between 276 G>T and HOMA IR |
| 7 | Shin et al., 2006 | 1.91 ± 0.07 | 2.08 ± 0.19 (G/T +T/T) | 2.08 ± 0.19 (G/T +T/T) | 2.64 ± 0.18  (G/G)  2.24 ±0.14  (G/T+T/T) | <0.001 | Positive Association was observed between GG homozygotes at SNP 276 and HOMA IR |

(SNP 276 G>T– Single nucleotide polymorphism of 276 allele present in Anorexia nervosa affecting Insulin sensitivity; AMP1- The Arabidopsis AMP1 gene; ADIPOQ gene- Adiponectin gene; IR- Insulin Resistance; HOMA -IR – Homeostatic Model of Insulin Resistance; p value – p Value for HOMA -IR)

***Findings of Studies and Data Analysis***

**TABLE 1: Table of Characteristics:**

The table encompasses a comprehensive array of studies investigating the relationship between ADIPOQ (Adiponectin) and increased insulin sensitivity in Anorexia Nervosa (AN) patients, as well as research into polymorphisms within the ADIPOQ gene associated with impaired insulin sensitivity in this population. Spanning from 1st July 2004 to 3rd July 2021, these studies were conducted across diverse locations such as Cambridge, Kyoto, Prague, Seoul, Boston, Yantai, Athens, Warsaw, and Zulia state, with sample sizes ranging from 7 to 308 AN patients and varying healthy control group sizes. The majority of studies were cross-sectional, complemented by one cohort study and two case-control study. The primary domains measured included HOMA IR (Homeostatic Model Assessment of Insulin Resistance) and ApN (Adiponectin) levels, alongside genetic polymorphisms within the ADIPOQ gene. Regarding tools used, RIA (Radioimmunoassay) kits were predominantly employed for ApN measurement, utilized in 9 out of 10 papers. Additionally, ELISA (Enzyme-Linked Immunosorbent Assay) kits were used in 4 out of 15 papers for ApN measurement. For genetic analysis related to ADIPOQ polymorphisms, genomic DNA purification kits were used in 3 out of 7 papers, while Taq man assays and DNA salting out methods were utilized in 1 out of 7 papers each. The JBI (Joanna Briggs Institute) Tool Score ranged from 5 to 8 out of 8, reflecting varying methodological quality across the studies. This collective analysis underscores a robust exploration of ADIPOQ's role and genetic variations concerning insulin sensitivity in AN patients.

**TABLE 2 : Categorisation of Findings of the studies**

This table categorizes the findings of various studies on three key associations within the context of Anorexia Nervosa (AN): Adiponectin levels in AN patients and Homeostatic Model Assessment of Insulin Resistance (HOMA IR), the association of the +45 allele with HOMA IR, and the association of the +276 allele with HOMA IR.

Regarding Adiponectin levels in AN patients and HOMA IR, the studies present a spectrum of associations. Dostálová I et al. (2006) revealed a positive association, indicating a beneficial relationship between Adiponectin levels and insulin sensitivity. In contrast, Tagami et al. (2004), Housova et al. (2005), and R. Dolezalova et al. (2007) reported a more moderate association. Interestingly, Misra et al. (2004) and Misra et al. (2007) found no significant association, albeit the latter noted low insulin resistance levels in AN patients.

Moving to the +45 allele's association with HOMA IR, Melistas et al. (2009) and Karolina Natalia Ziora-Jakutowicz et al. (2021) provided evidence supporting a meaningful connection. On the other hand, Prakash et al. (2015) and Sánchez et al. (2022) reported a less pronounced association. Shin et al. (2006) observed a weak association, while N Zhang et al. (2008) did not find a significant correlation.

Lastly, the +276 allele's relationship with HOMA IR showed varied results. Shin et al. (2006), Karolina Natalia Ziora-Jakutowicz et al. (2021), and Melistas et al. (2009) demonstrated a strong association, suggesting a notable impact on insulin sensitivity. In contrast, N Zhang et al. (2008) and Prakash et al. (2015) noted a less prominent association. Kim et al. (2010), however, found no meaningful connection between the +276 allele and HOMA IR.This comprehensive categorization provides valuable insights into the diverse relationships between Adiponectin levels, genetic alleles, and insulin resistance in AN patients, contributing significantly to the understanding of metabolic dynamics in this population.

Top of Form**TABLE 3 : DATA FOR ASSOCIATION OF HOMA IR WITH ADIPONECTIN IN AN PATIENTS:**

The comprehensive analysis of studies investigating the association between Adiponectin levels and Homeostatic Model Assessment of Insulin Resistance (HOMA IR) in Anorexia Nervosa (AN) patients reveals a nuanced picture of metabolic dynamics in this population. Tagami et al. (2004) and R. Dolezalova et al. (2007) highlighted significant associations between Adiponectin levels and HOMA IR, indicating that hyperadiponectinemia may contribute to increased insulin sensitivity (IS) in AN, as supported by Dostálová et al. (2006). However, the studies by Misra et al. (2004, 2007) and Křížová et al. (2008) did not find a direct correlation between HOMA IR and Adiponectin levels. Notably, Tagami et al. (2004) reported reduced insulin resistance indices and Adiponectin levels in AN patients compared to controls, suggesting the involvement of additional factors like leptin, TNF, and resistin in determining insulin resistance.

Furthermore, the collective findings from the table underscore the intricate interplay between Adiponectin levels, other adipokines, and insulin sensitivity in AN patients. R. Dolezalova et al. (2007) highlighted the role of altered Adiponectin production and dysregulated adipokines in local metabolic alterations and HOMA IR. Dostálová et al. (2006) observed significantly altered plasma adipokine levels, particularly hyperadiponectinemia, contributing to increased insulin sensitivity in AN.In conclusion, while some studies suggest a link between Adiponectin levels and improved insulin sensitivity in AN, the overall understanding remains complex. Additional research is crucial to unravel the precise mechanisms and implications of these relationships, which could potentially aid in the management and treatment of metabolic alterations in AN patients.

**TABLE 4 AND 5: DATA FOR ASSOCIATION +45 T>G**

The investigation into ADIPOQ polymorphisms, specifically +45 T>G and +276 G>T, in relation to Homeostatic Model Assessment of Insulin Resistance (HOMA IR) yielded varied results across studies. Table 4 outlines associations with the +45 T>G polymorphism, with Shin et al. (2006) reporting a significant decrease in HOMA IR, while N Zhang et al. (2008) found no significant association. Conversely, Melistas et al. (2009) and Karolina Natalia Ziora-Jakutowicz et al. (2021) noted a substantial correlation between +45 T>G polymorphism and HOMA IR. Table 5 details associations with the +276 G>T polymorphism, where Shin et al. (2006), Karolina Natalia Ziora-Jakutowicz et al. (2021), and Melistas et al. (2009) observed a significant association with HOMA IR, while Prakash et al. (2015) and Zhang et al. (2008) reported moderate associations. However, Kim et al. (2010) and Song et al. (2018) identified poor or no associations. Overall, both polymorphisms exhibit some influence on HOMA IR collectively suggesting a complex relationship between ADIPOQ polymorphisms, particularly +45 T>G and +276 G>T, and HOMA IR These findings underscore the complexity of genetic variations in modulating insulin resistance and highlight the need for further research to elucidate their precise mechanisms and clinical implication.

**DISCUSSION:**

This study demonstrates several strengths that significantly contribute to understanding the complex metabolic dynamics in Anorexia Nervosa (AN) patients. Firstly, the research undertakes a meticulous and comprehensive analysis of multiple research papers, providing an extensive overview of the association between Adiponectin levels, genetic polymorphisms in the ADIPOQ gene, and Homeostatic Model Assessment of Insulin Resistance (HOMA IR) in AN patients. This comprehensive approach ensures a holistic understanding of metabolic interactions in this unique population.

Secondly, by encompassing various studies with divergent findings, the research captures diverse perspectives and nuances concerning the relationship between Adiponectin, insulin sensitivity, and genetic variations. This inclusivity contributes significantly to a deeper comprehension of the complex metabolic interactions in AN patients.

Thirdly, the study's findings have practical implications for clinical practice by shedding light on potential biomarkers and genetic factors that could influence insulin sensitivity and overall metabolic health in AN patients. This insight is crucial for devising targeted and personalized treatment strategies.

Despite its strengths, this study faces certain limitations that warrant consideration. The included studies exhibit variability in terms of sample sizes, methodologies, and patient populations, leading to potential heterogeneity in the results. This diversity may limit direct comparisons and necessitate cautious interpretation of the findings.

Additionally, some studies may lack comprehensive data on certain variables, potentially resulting in gaps in the analysis and interpretation of results. This limitation underscores the importance of robust data collection and standardization across studies.

Furthermore, many of the included studies are cross-sectional in design, which limits the ability to establish causality or discern long-term effects of Adiponectin levels and genetic polymorphisms on insulin sensitivity in AN patients. Longitudinal studies would provide more insights into temporal relationships.

The main outcomes of the study encompass the diverse associations observed between Adiponectin levels, genetic polymorphisms +45 T>G and +276 G>T in the ADIPOQ gene, and HOMA IR in AN patients. These findings underscore the complexity of genetic variations in modulating insulin resistance and highlight the need for further research to elucidate their precise mechanisms and clinical implications. One of the proposed mechanisms is that ADIPOQ gene polymorphisms can influence insulin sensitivity in AN patients primarily by modulating adiponectin levels. Higher adiponectin levels are associated with improved insulin sensitivity, reduced inflammation, and better energy balance, which are crucial in the metabolic context of anorexia nervosa.

In conclusion, while some studies suggest a link between Adiponectin levels and improved insulin sensitivity in AN, the overall understanding remains complex. Overall, both polymorphisms exhibit some influence on HOMA IR collectively suggesting a complex relationship between ADIPOQ polymorphisms, particularly +45 T>G and +276 G>T, and HOMA IR Additional research is crucial to unravel the precise mechanisms and implications of these relationships, which could potentially aid in the management and treatment of metabolic alterations in AN patients.

Recent studies focusing on the association of ADIPOQ/Adiponectin with insulin sensitivity in Anorexia Nervosa (AN) patients and the identification of ADIPOQ gene polymorphisms and their link to impaired insulin sensitivity in AN patients have made significant contributions to understanding metabolic dynamics in this population.

One notable study by Radka Dolezalova et al. (2007) compared circulating levels of adipocytokines versus subcutaneous mRNA expression in AN patients. They found local perturbations in resistin, adiponectin, and interleukin-6 mRNA expression in subcutaneous adipose tissue, suggesting potential local metabolic disturbances. This study aligns with our research by emphasizing the complex metabolic interactions within AN patients, albeit focusing on different aspects of adipocytokines.

In another study by I. Dostálová et al. (2006), researchers observed increased insulin sensitivity in AN patients, accompanied by reduced plasma insulin levels and low HOMA-R index. This finding is consistent with our research, which also indicates a relationship between Adiponectin levels and improved insulin sensitivity in AN patients.

M. L. Delporte et al. (2003) investigated hyperadiponectinemia in AN patients and found increased plasma adiponectin levels, which may contribute to maintaining enhanced insulin sensitivity. One possible mechanism suggested could be individuals with low body fat, the adipocytes (fat cells) might compensate by increasing the secretion of adiponectin to enhance insulin sensitivity and mobilize energy stores. This aligns with our study's focus on Adiponectin and its implications for insulin sensitivity in AN patients. Additionally, Tetsuya Tagami et al. (2003) reported lower serum adiponectin levels in AN patients but increased insulin sensitivity. This contrasts with some aspects of our findings, highlighting the complexity and variability in metabolic responses within AN populations.

Furthermore, studies by Toshihiro Nakahara et al. (2008) and Dalit Modan-Moses et al. (2007) also explored metabolic changes, including adiponectin levels, during refeeding and weight rehabilitation in AN patients. These studies provide insights into the dynamic nature of metabolic adaptations in AN, which aligns with our emphasis on understanding long-term implications and treatment strategies.

Regarding genetic polymorphisms, studies by N. Zhang et al. and Melistas et al. investigated specific ADIPOQ gene variants and their associations with insulin resistance. These studies complement our research by highlighting the role of genetic factors in modulating insulin sensitivity in different populations.

Comparatively, our research fares better by providing a comprehensive synthesis of recent studies, reconciling conflicting findings, and emphasizing personalized medicine approaches tailored to genetic variations in managing insulin resistance and metabolic health in AN patients. Our study bridges gaps, enhances understanding of metabolic dysregulation, and identifies areas for future investigation, contributing significantly to the field's advancement.

In conclusion, recent studies in the field of ADIPOQ/Adiponectin and insulin sensitivity in AN patients have provided valuable insights into metabolic dynamics and genetic influences. While these studies contribute essential pieces to the puzzle, our research extends further by integrating diverse perspectives, offering a comprehensive analysis, and emphasizing the need for personalized medicine in managing metabolic challenges in AN.

Moreover, the study's emphasis on personalized medicine approaches and genetic screening aligns with Sustainable Development Goals (SDGs), particularly SDG 3 - Good Health and Well-being. The findings may inform policies related to personalized medicine, genetic screening strategies, and tailored metabolic health interventions, ultimately contributing to improved health outcomes and quality of life in vulnerable populations like AN patients.

**CONCLUSION**In summary, despite certain research indicating a connection between elevated Adiponectin levels and enhanced insulin sensitivity in individuals with AN, the complete picture is still unclear. All things considered, both polymorphisms have some effect on HOMA IR, collectively pointing to a complex link between HOMA IR and ADIPOQ polymorphisms, specifically +45 T>G and +276 G>T.

**RECOMMENDATIONS**Future studies should use standardised techniques to lower variability and bigger, more varied sample sizes in order to improve this thesis. To prove causation and comprehend the long-term impacts of Adiponectin levels and ADIPOQ polymorphisms on insulin sensitivity in AN patients, longitudinal research are required. Furthermore, combining personalised medicine techniques with improved genetic screening can improve our knowledge of metabolic dynamics and help us create more focused treatment plans. Highlighting these elements will support the study's findings and

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