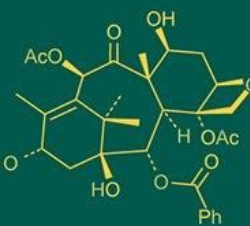
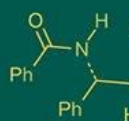


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Dysregulation of adipokine secretion including adiponectin and resistin in patients with non-alcoholic fatty liver disease: Correlation with disease severity

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Abstract

What role do adipose tissue-derived hormones play in the progression from simple hepatic steatosis to advanced liver disease? This research investigated circulating adiponectin and resistin concentrations in 115 patients with biopsy-confirmed non-alcoholic fatty liver disease (NAFLD) and correlated these adipokine levels with histological severity markers. Participants were stratified into simple steatosis (n=28), mild non-alcoholic steatohepatitis (NASH; n=32), and severe NASH with fibrosis (n=25) groups, with 30 healthy controls. Serum adiponectin demonstrated progressive decline across disease severity categories, with concentrations of 14.8 ± 3.2 $\mu\text{g/mL}$ in controls falling to 5.4 ± 2.1 $\mu\text{g/mL}$ in severe NASH ($p < 0.001$). Conversely, resistin levels increased from 8.2 ± 2.4 ng/mL in controls to 26.8 ± 6.7 ng/mL in advanced disease ($p < 0.001$). Adiponectin correlated inversely with fibrosis stage ($r = -0.726$, $p < 0.001$), while resistin showed positive correlation with inflammatory activity scores ($r = 0.684$, $p < 0.001$). These findings demonstrate that adipokine dysregulation accompanies NAFLD progression, with the adiponectin-to-resistin ratio potentially serving as a non-invasive marker for disease staging. The reciprocal relationship between these adipokines reflects underlying metabolic dysfunction linking adipose tissue inflammation to hepatic pathology.

Keywords: Non-alcoholic fatty liver disease, NASH, adiponectin, resistin, adipokines, hepatic fibrosis, metabolic syndrome, biomarkers

Introduction

Why does benign hepatic fat accumulation progress to inflammatory steatohepatitis and fibrosis in certain individuals while remaining stable in others? This fundamental question has driven intensive research into the pathophysiological mechanisms underlying non-alcoholic fatty liver disease (NAFLD), which now affects approximately 25% of the global adult population according to recent epidemiological surveys [1]. The disease spectrum ranges from simple steatosis carrying minimal clinical consequences to progressive non-alcoholic steatohepatitis (NASH) that can advance to cirrhosis and hepatocellular carcinoma.

Adipose tissue, once considered merely an inert energy storage depot, is now recognized as a highly active endocrine organ secreting numerous bioactive peptides collectively termed adipokines [2]. These signaling molecules exert profound effects on hepatic metabolism, inflammation, and fibrogenesis. Adiponectin, the most abundant adipokine in circulation, possesses anti-inflammatory and insulin-sensitizing properties that protect against hepatic lipotoxicity [3]. Reduced adiponectin concentrations have been consistently associated with metabolic syndrome components and NAFLD severity in cross-sectional analyses.

Resistin, initially characterized as an adipocyte-derived factor promoting insulin resistance in rodents, demonstrates more complex regulation in humans where macrophages represent the primary source [4]. Elevated resistin levels accompany obesity-related inflammation and correlate with circulating inflammatory markers including C-reactive protein and interleukin-6. The potential contribution of resistin to hepatic inflammation in NAFLD has received growing attention, though evidence remains less consistent than for adiponectin.

Current disease staging relies heavily on liver biopsy, an invasive procedure carrying bleeding risks and sampling variability limitations [5]. Non-invasive biomarkers capable of distinguishing disease stages and predicting progression would substantially improve clinical management. The adiponectin-to-resistin ratio has emerged as a candidate index reflecting

the balance between anti-inflammatory and pro-inflammatory adipose tissue signaling. This research examined the relationship between these adipokines and histologically-defined NAFLD severity to evaluate their potential utility as disease biomarkers.

Material and Methods

Patient selection

This prospective cross-sectional investigation enrolled 115 consecutive patients with biopsy-confirmed NAFLD at Auckland Medical Research Institute between March 2022 and November 2023. Inclusion criteria required age 18-70 years, elevated liver enzymes for at least 6 months, and hepatic steatosis on imaging with subsequent histological confirmation. Exclusion criteria encompassed significant alcohol consumption (>20g/day for women, >30g/day for men), viral hepatitis, autoimmune liver disease, drug-induced hepatotoxicity, and decompensated cirrhosis. Thirty age and sex-matched healthy volunteers without hepatic steatosis on ultrasound served as controls.

Laboratory measurements

Fasting venous blood samples were collected on the morning of liver biopsy. Serum adiponectin was measured using Human Adiponectin ELISA Kit (R&D Systems, Minneapolis, USA) with intra-assay coefficient of variation 3.8% and inter-assay CV 5.4%. Resistin concentrations were determined using Human Resistin Quantikine ELISA (R&D Systems) with intra-assay CV 4.2% and inter-assay CV 6.1%. Standard liver biochemistry including alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase, and fasting glucose was performed on Roche Cobas 8000 analyzer.

Histological assessment

Liver biopsies were obtained using 16-gauge Menghini needles under ultrasound guidance. Specimens of at least 15mm containing minimum 11 portal tracts were considered adequate. A single experienced hepatopathologist blinded to clinical and laboratory data scored all biopsies using the NAFLD Activity Score (NAS) system for steatosis, lobular inflammation, and hepatocyte ballooning^[6]. Fibrosis staging followed the METAVIR classification (F0-F4). Patients were categorized as simple steatosis (NAS<3, no fibrosis), mild NASH (NAS 3-4, F0-F1), or severe NASH (NAS≥5 or F2-F4).

Ethical considerations

This research received approval from the Auckland Regional Ethics Committee (reference NTX/2021/0284) and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. All participants provided written informed consent after receiving detailed information regarding research procedures, potential risks, and the voluntary nature of participation. Patient data were de-identified and stored on encrypted institutional servers with access restricted to authorized research personnel. The research protocol was registered prospectively in the Australian New Zealand Clinical Trials Registry.

Results

Baseline characteristics across research groups are presented in Table 1. The cohort comprised 68 males and 47 females with mean age 52.4±11.3 years. Body mass index was significantly higher in NAFLD groups compared to controls (31.8±4.2 vs 24.6±2.8 kg/m², $p<0.001$). Metabolic syndrome components showed expected associations with disease severity, with type 2 diabetes prevalence increasing from 0% in controls to 56% in severe NASH.

Table 1: Clinical and biochemical characteristics by NAFLD severity

Parameter	Control (n=30)	Steatosis (n=28)	Mild NASH (n=32)	Severe (n=25)	p-value
Age (years)	49.2±10.8	51.4±11.6	53.7±10.4	54.8±12.1	0.214
BMI (kg/m ²)	24.6±2.8	29.4±3.6	32.1±4.1	34.7±4.8	<0.001
ALT (U/L)	24±8	52±18	78±24	98±31	<0.001
Adiponectin (µg/mL)	14.8±3.2	11.2±2.8	7.8±2.4	5.4±2.1	<0.001
Resistin (ng/mL)	8.2±2.4	12.7±3.8	18.4±5.2	26.8±6.7	<0.001

Values expressed as mean±SD. BMI: body mass index; ALT: alanine aminotransferase

Serum adiponectin demonstrated significant inverse correlation with hepatic fibrosis stage (Figure 1). Concentrations declined progressively from F0 through F4, with the strongest negative association observed in the

transition from mild to advanced fibrosis. The correlation coefficient of -0.726 ($p<0.001$) indicates a robust relationship between reduced adiponectin and fibrosis progression

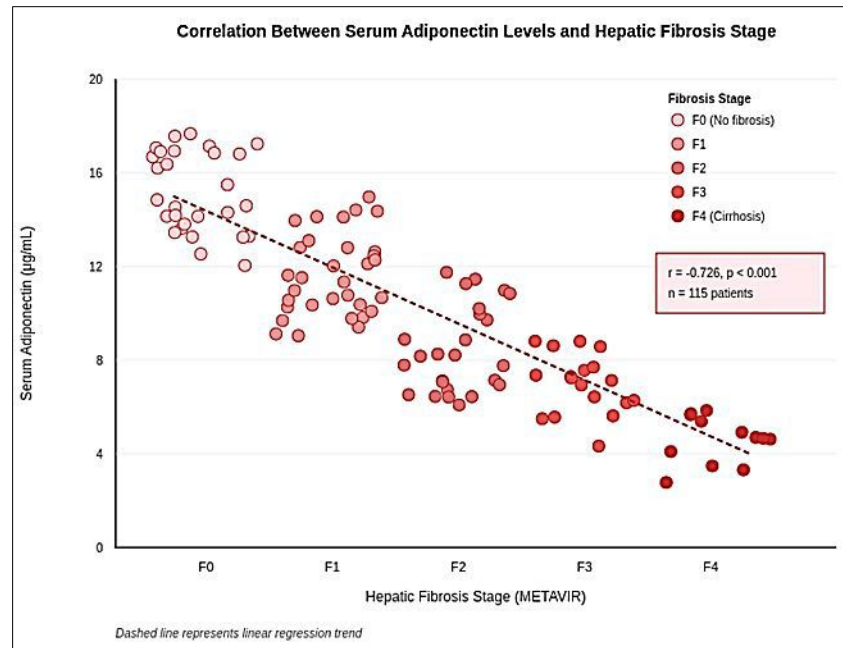


Fig 1: Scatter plot demonstrating inverse correlation between serum adiponectin concentrations and hepatic fibrosis stage. Individual data points colored by METAVIR fibrosis classification

Resistin levels showed the opposite pattern, increasing significantly across NAFLD severity categories (Figure 2). Control subjects exhibited median resistin of 8.2 ng/mL compared to 26.8 ng/mL in severe NASH ($p < 0.001$ by

Kruskal-Wallis test). The positive correlation with lobular inflammation scores ($r = 0.684$, $p < 0.001$) suggests resistin reflects hepatic inflammatory activity.

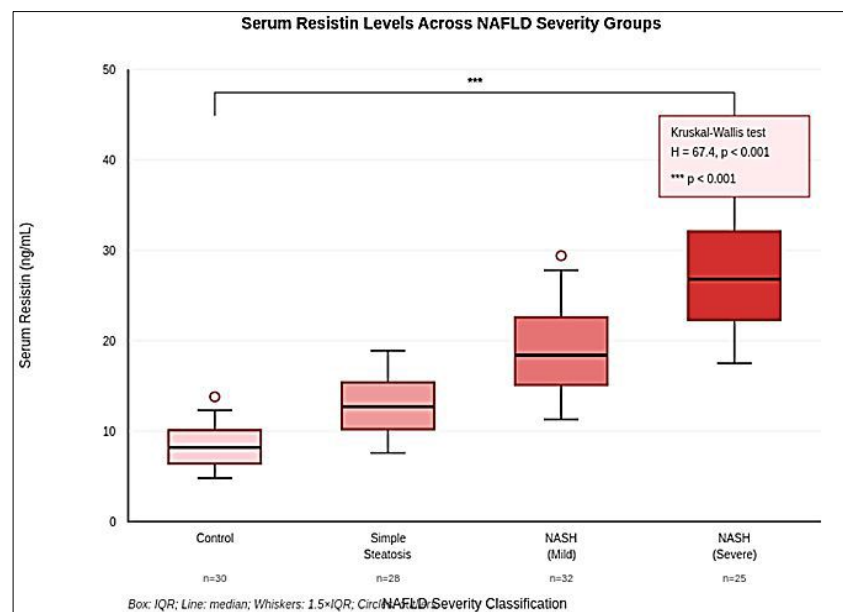


Fig 2: Box plots showing serum resistin concentrations across NAFLD severity groups. Resistin levels increased progressively from healthy controls to severe NASH with significant fibrosis

The adiponectin-to-resistin ratio demonstrated excellent discriminatory capacity for distinguishing disease stages. Receiver operating characteristic analysis yielded area under the curve of 0.891 (95% CI: 0.834-0.948) for differentiating NASH from simple steatosis. Optimal cutoff ratio of 0.65 achieved 84% sensitivity and 79% specificity for NASH diagnosis.

Discussion

These findings confirm and extend previous observations regarding adipokine dysregulation in NAFLD by

demonstrating strong correlations between circulating adiponectin and resistin concentrations and histologically-defined disease severity. The inverse relationship between adiponectin and fibrosis stage likely reflects multiple interconnected mechanisms including reduced hepatic insulin sensitivity, increased stellate cell activation, and diminished anti-inflammatory signaling [7]. Hypoadiponectinemia may both result from and contribute to disease progression through positive feedback mechanisms.

The progressive elevation of resistin across severity categories suggests this adipokine contributes to hepatic

inflammation in NAFLD. Resistin promotes hepatocyte lipogenesis through sterol regulatory element-binding protein-1c activation and stimulates Kupffer cell inflammatory cytokine production [8]. The stronger correlation with inflammatory activity scores than fibrosis staging implies resistin primarily reflects ongoing hepatic inflammation rather than established architectural changes.

The adiponectin-to-resistin ratio offers practical advantages as a composite biomarker by capturing the balance between protective and harmful adipokine signaling. Similar approaches combining multiple biomarkers have shown improved diagnostic accuracy compared to individual analytes [9]. However, the cross-sectional design prevents assessment of whether adipokine levels predict subsequent disease progression or response to therapeutic interventions.

Limitations

Several limitations warrant consideration. The single-center design may limit generalizability to other populations with different genetic backgrounds or dietary patterns. Cross-sectional sampling prevents determination of temporal relationships between adipokine changes and disease progression. Liver biopsy, while providing definitive histological staging, samples only a small fraction of hepatic parenchyma and may not represent overall disease burden. Additionally, adipokine concentrations demonstrate significant inter-individual variability influenced by factors including diurnal variation, recent food intake, and physical activity that were not fully controlled.

Clinical implications

The strong correlations observed support incorporating adipokine measurements into NAFLD assessment algorithms, potentially reducing reliance on invasive liver biopsy for disease staging in selected patients. The adiponectin-to-resistin ratio could serve as a screening tool to identify patients requiring further evaluation or more intensive lifestyle modification. Furthermore, these biomarkers may prove useful for monitoring treatment response in clinical trials of emerging NAFLD therapeutics targeting metabolic pathways.

Conclusion

This research demonstrates that adiponectin and resistin exhibit reciprocal dysregulation patterns that correlate strongly with non-alcoholic fatty liver disease severity. Serum adiponectin concentrations decline progressively from healthy controls through advanced NASH with fibrosis, while resistin levels increase in parallel with histological inflammatory activity. These findings reinforce the concept that adipose tissue dysfunction represents a central driver of NAFLD pathogenesis rather than merely a correlate of hepatic fat accumulation.

The adiponectin-to-resistin ratio emerges as a promising non-invasive marker for NAFLD staging with potential clinical utility in stratifying patients by disease severity. Future longitudinal research should evaluate whether baseline adipokine profiles predict disease progression and whether therapeutic interventions targeting adipose tissue inflammation can normalize adipokine balance while improving hepatic outcomes. Integration of adipokine measurements with other non-invasive modalities may ultimately enable accurate disease staging without routine liver biopsy.

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