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ORIGINAL RESEARCH

Physiological effects of Intermittent fasting on glucose homeostasis and Insulin Sensitivity

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Abstract

Aim: The aim of this study was to investigate the physiological effects of intermittent fasting on glucose homeostasis and insulin sensitivity in healthy individuals, focusing on markers such as fasting glucose, fasting insulin, HOMA-IR, and the Matsuda Index.

Materials and Methods: This Prospective study included 100 participants was conducted in 2018 in GMC Jammu, with equal distribution across gender and age groups (20–50 years), all with a BMI in the normal range. Participants followed a 16:8 intermittent fasting regimen (16 hours of fasting with an 8-hour feeding window) while maintaining standardized dietary intake and physical activity. Data were collected at baseline, midpoint (6 weeks), and endpoint (12 weeks) on fasting glucose, fasting insulin, HOMA-IR, and the Matsuda Index. OGTT tests were conducted at baseline and endpoint to assess glucose tolerance. Repeated-measures ANOVA was used to analyze changes over time, and regression analysis examined correlations in glucose and insulin response.

Results: Over the study period, intermittent fasting significantly reduced fasting glucose (95.2 mg/dL at baseline to 87.5 mg/dL at endpoint, $p<0.001$) and fasting insulin (10.5 μU/mL to 8.6 μU/mL, $p=0.001$). HOMA-IR showed a marked decline, indicating improved insulin sensitivity. OGTT results at the endpoint showed a significant reduction in glucose levels across all time points (0, 30, 60, and 120 minutes), highlighting improved glucose tolerance. The Matsuda Index increased significantly, from 3.2 at baseline to 4.5 at the endpoint ($p<0.001$), confirming enhanced insulin sensitivity. Regression analysis demonstrated strong correlations in glucose and insulin response changes over time, further supporting the beneficial effects of intermittent fasting on metabolic health.

Conclusion: Intermittent fasting positively impacts glucose homeostasis and insulin sensitivity, as evidenced by reductions in fasting glucose, fasting insulin, HOMA-IR, and improved Matsuda Index scores. These findings suggest that intermittent fasting can be an effective and practical approach to improve metabolic health in healthy adults, with potential applications for preventing metabolic disorders.

Keywords: Intermittent fasting, Glucose homeostasis, Insulin sensitivity, HOMA-IR, Matsuda Index

Introduction

Intermittent fasting (IF) has gained significant attention as a dietary approach that involves cycling between periods of eating and fasting, typically without the restriction of specific food types or a reduction in total caloric intake over time. This dietary strategy has been

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studied for its potential benefits on various metabolic parameters, particularly concerning glucose homeostasis and insulin sensitivity. Glucose homeostasis, or the body's ability to regulate blood sugar levels within a narrow range, is essential for maintaining overall metabolic health and preventing metabolic diseases such as type 2 diabetes. Similarly, insulin sensitivity—how effectively cells respond to insulin in regulating blood glucose levels—plays a crucial role in energy metabolism and is a key factor in metabolic disorders when dysregulated.[1]The most common IF protocols include alternate-day fasting, time-restricted feeding, and periodic fasting. Alternate-day fasting involves alternating between fasting days, where little to no food is consumed, and non-fasting days, where food intake is typically unrestricted. Time-restricted feeding limits food intake to a specific window each day, such as eating only within an eight-hour period, followed by 16 hours of fasting, commonly referred to as the 16:8 method. Periodic fasting, on the other hand, involves fasting for a more extended period, such as 24 hours, once or twice a week. These variations in fasting regimens have distinct effects on physiological processes, and their impacts on glucose and insulin dynamics have become an area of intense study.[2]The mechanism behind IF's effects on glucose and insulin dynamics is believed to involve several metabolic pathways. During fasting, the body's glycogen stores in the liver are depleted, and it begins to rely on lipolysis, or fat breakdown, as a primary energy source. This metabolic switch from glucose to fatty acids for energy can lead to reduced insulin levels, as there is less need for insulin to facilitate glucose uptake by cells. Additionally, fasting is associated with reduced levels of inflammatory markers and oxidative stress, both of which have been linked to insulin resistance. Lower inflammation levels may improve insulin sensitivity, allowing cells to utilize glucose more efficiently. Consequently, IF may help regulate blood glucose levels by improving the body's response to insulin, which could potentially prevent or even reverse insulin resistance in some individuals.[3]Furthermore, IF may impact glucose homeostasis and insulin sensitivity through changes in the secretion of key hormones, including glucagon and growth hormone. Glucagon, which promotes the breakdown of glycogen in the liver to release glucose, is typically elevated during fasting periods, helping to maintain stable blood glucose levels in the absence of food intake. Growth hormone, which also rises during fasting, aids in preserving lean body mass and mobilizing fat for energy, further supporting the shift toward fat metabolism. By influencing these hormonal responses, IF may contribute to improved glucose stability and enhanced insulin sensitivity over time.[4]

The physiological effects of IF on glucose regulation can also be assessed through biomarkers such as fasting glucose, insulin, and Hemoglobin A1c (HbA1c) levels, as well as indices like the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR). These markers provide insight into how IF might influence metabolic health, especially regarding insulin sensitivity. The Oral Glucose Tolerance Test (OGTT) and the Matsuda Index, which measure glucose clearance and insulin sensitivity, respectively, are also valuable tools for assessing the long-term impacts of IF on glucose metabolism. Numerous studies have demonstrated that intermittent fasting may lead to a reduction in fasting glucose and insulin levels, which indicates an improvement in the body's ability to regulate glucose with lower insulin demands. Additionally, some research suggests that IF may lower HbA1c levels, which is a marker of long-term blood glucose control, thereby potentially reducing the risk of diabetes and other metabolic disorders.[5]Aside from glucose regulation, intermittent fasting has been associated with beneficial effects on body composition, specifically regarding weight loss and fat reduction. Reductions in body fat, especially visceral fat, are linked to improved insulin sensitivity, as excess fat can contribute to insulin resistance. By promoting a healthier body composition, IF indirectly supports better glucose homeostasis and may further enhance insulin sensitivity. This body composition change can have significant implications for individuals with obesity or metabolic syndrome, as weight loss alone is a

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powerful tool in restoring normal glucose regulation and reducing insulin resistance.[6]Moreover, IF is thought to positively influence circadian rhythms, which are the body's natural cycles of physiological processes that follow a 24-hour period. Eating and fasting in alignment with circadian rhythms may support glucose homeostasis, as insulin sensitivity naturally fluctuates throughout the day. For example, studies have shown that insulin sensitivity is typically higher in the morning than in the evening, suggesting that aligning food intake with the body's natural rhythm could optimize metabolic outcomes. Time-restricted feeding, a popular IF method, takes advantage of this concept by confining food intake to earlier hours in the day, which may further enhance glucose regulation and insulin sensitivity.[7,8]The growing interest in intermittent fasting and its effects on glucose homeostasis and insulin sensitivity highlights its potential as a dietary intervention for metabolic health. Compared to continuous calorie restriction, which can be difficult to maintain over the long term, IF is often perceived as a more sustainable approach. By focusing on the timing of food intake rather than caloric reduction, IF may be more accessible and manageable for individuals aiming to improve their metabolic health without drastically altering their diet. This approach could have significant implications for individuals at risk of or managing conditions such as obesity, insulin resistance, and type 2 diabetes.

Materials and Methods

This prospective study was conducted in 2018 in GMC Jammuto investigate the physiological effects of intermittent fasting on glucose homeostasis and insulin sensitivity. A total of 100 participants were enrolled, with an equal distribution of males and females, aged between 20 and 50 years. Participants were selected based on inclusion and exclusion criteria to ensure general health and no prior history of diabetes or insulin resistance.This study was approved by the Institutional Ethics Committee. Written informed consent was obtained from all participants before enrollment. Participants were assured of confidentiality and the option to withdraw from the study at any point without consequence

Inclusion and Exclusion Criteria

Inclusion criteria included individuals with a BMI within the normal range (18.5-24.9 kg/m^2), non-smokers, not on any medication that could affect insulin sensitivity or glucose metabolism, and those who had not participated in any form of fasting or restricted diet in the past six months. Exclusion criteria included individuals with a history of metabolic disorders, cardiovascular diseases, pregnancy, lactation, and individuals on medications affecting glucose or lipid metabolism.

Methodology

Participants were assigned to follow an intermittent fasting regimen of 16 hours of fasting followed by an 8-hour feeding window daily for 12 weeks. During the fasting period, participants were only allowed to consume water and calorie-free beverages. Meals during the feeding window were standardized and monitored for calorie intake, macronutrient distribution, and portion control to maintain a balanced diet based on each participant's basal metabolic rate (BMR) requirements.

Data Collection and Laboratory Measurements

Baseline Measurements: At the beginning of the study, participants underwent baseline assessments, which included fasting blood glucose, fasting insulin, HbA1c, and HOMA-IR (Homeostatic Model Assessment of Insulin Resistance) to measure insulin sensitivity. Anthropometric measurements, including weight, height, BMI, and waist circumference, were also recorded.

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Midpoint and Endpoint Assessments: These measurements were repeated at the 6-week (midpoint) and 12-week (endpoint) marks to observe changes over time. Additionally, blood samples were collected at baseline, midpoint, and endpoint for laboratory analysis.
Blood Glucose and Insulin Levels: Blood glucose levels were measured using an enzymatic method, and fasting insulin levels were determined using a chemiluminescence immunoassay. HOMA-IR was calculated as a marker of insulin sensitivity using the formula:
HOMA-IR=Fasting Insulin (\muU/ml) x Fasting Glucose (mg/dl)405\text{HOMA-IR} = \frac{\text{Fasting Insulin (\mu U/ml) x Fasting Glucose (mg/dl)}}{405}HOMA-IR=405Fasting Insulin (\muU/ml) x Fasting Glucose (mg/dl)
Oral Glucose Tolerance Test (OGTT): An OGTT was performed at baseline and after 12 weeks. Participants were given a 75g glucose solution after an overnight fast, and blood samples were drawn at 0, 30, 60, and 120 minutes to assess glucose and insulin response over time.
Insulin Sensitivity Assessment: Insulin sensitivity was assessed using the Matsuda Index, calculated from OGTT data, providing a comprehensive measure of glucose disposal.
Dietary and Physical Activity Monitoring: Participants were provided with dietary guidelines to follow during the feeding window to ensure calorie consistency. Compliance with the fasting protocol was monitored using daily logs and weekly check-ins. Physical activity was also recorded to control for exercise as a confounding variable. Participants were asked to maintain their usual activity levels and avoid significant changes in physical activity routines.
The primary outcome measures were changes in fasting glucose, fasting insulin, HOMA-IR, and the Matsuda Index. Secondary outcomes included changes in anthropometric measurements and OGTT results to assess insulin response and glucose tolerance.

Statistical Analysis
All data were recorded and analyzed using SPSS Version 25.0. Results were expressed as mean ± standard deviation. Paired t-tests were used to compare baseline and endpoint measures, while repeated-measures ANOVA was applied to analyze changes over time at baseline, midpoint, and endpoint. Pearson correlation coefficients were calculated to assess the relationship between fasting insulin and glucose levels. A p-value of <0.05 was considered statistically significant.

Results
Table 1: Demographic Characteristics of Study Participants
The study included 100 participants, with an equal gender distribution of 50 males and 50 females. Participants were evenly distributed across three age groups: 20-29 years (32%), 30-39 years (35%), and 40-50 years (33%). The BMI distribution showed that 42% of participants had a BMI between 18.5-22.0 kg/m², while 58% had a BMI of 22.1-24.9 kg/m², indicating all participants were within the normal BMI range. All participants were non-smokers, and physical activity levels varied, with 28% at a low level, 47% at a moderate level, and 25% at a high level.
Table 2: Anthropometric Measurements Over Time
Anthropometric measurements, including weight, BMI, and waist circumference, were recorded at baseline, 6 weeks (midpoint), and 12 weeks (endpoint). Over the study period, weight showed a statistically significant reduction (ANOVA $F=4.15$, $p=0.019$), with participants experiencing an average weight decrease from 72.3 kg to 70.5 kg by the endpoint. BMI decreased correspondingly (ANOVA $F=5.33$, $p=0.007$), dropping from 23.5 to 22.9 kg/m², and waist circumference showed a significant reduction from 82.1 cm to 80.1 cm (ANOVA $F=6.27$, $p=0.004$), indicating an overall improvement in body composition.

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Table 3: Fasting Glucose, Insulin Levels, and HOMA-IR Over Time

Intermittent fasting significantly impacted glucose metabolism and insulin sensitivity. Fasting glucose levels decreased progressively from 95.2 mg/dL at baseline to 87.5 mg/dL at 12 weeks (ANOVA $F=8.92$, $p<0.001$). Fasting insulin also showed a significant reduction from 10.5 to 8.6 μU/mL (ANOVA $F=7.45$, $p=0.001$), reflecting improved insulin sensitivity. Similarly, HOMA-IR, an indicator of insulin resistance, decreased from 2.47 to 1.84 (ANOVA $F=9.11$, $p<0.001$), suggesting enhanced insulin sensitivity as a result of intermittent fasting.

Table 4: Oral Glucose Tolerance Test (OGTT) at Baseline and Endpoint

The OGTT results demonstrated significant improvements in glucose tolerance over the study period. At baseline, glucose levels were highest at 30 minutes post-ingestion (140.3 mg/dL) and reduced progressively over time, reaching 105.8 mg/dL at 120 minutes. By the endpoint, glucose levels were consistently lower across all time intervals: 0 minutes (87.5 mg/dL), 30 minutes (125.2 mg/dL), 60 minutes (115.4 mg/dL), and 120 minutes (95.0 mg/dL). These changes were statistically significant, with p-values <0.001 for the 0, 30, and 60-minute readings and $p=0.002$ for the 120-minute reading, indicating improved glucose clearance and tolerance due to the fasting intervention.

Table 5: Insulin Sensitivity (Matsuda Index) Over Time

The Matsuda Index, a measure of insulin sensitivity, significantly increased over the study duration. Starting at a baseline value of 3.2, it rose to 4.1 at the midpoint and reached 4.5 by the endpoint (ANOVA $F=13.79$, $p<0.001$), indicating enhanced insulin sensitivity. This improvement further corroborates the favorable effects of intermittent fasting on glucose regulation.

Table 6: Regression Analysis of Changes in Glucose and Insulin Response

Regression analysis revealed strong correlations in glucose and insulin responses over time. Fasting glucose levels decreased significantly from baseline to midpoint ($\beta=-0.62$, $p<0.001$) and from baseline to endpoint ($\beta=-0.64$, $p<0.001$), with a moderate decrease from midpoint to endpoint ($\beta=-0.58$, $p<0.001$). Fasting insulin levels and HOMA-IR both followed similar trends, with significant decreases over all intervals. The Matsuda Index showed positive regression coefficients across all intervals, indicating consistent improvements in insulin sensitivity ($\beta=0.61$, baseline vs. midpoint; $\beta=0.63$, baseline vs. endpoint; $\beta=0.59$, midpoint vs. endpoint; $p<0.001$ for all comparisons).

Table 1: Demographic Characteristics of Study Participants

Characteristic	Frequency (n=100)	Percentage (%)
Gender		
Male	50	50%
Female	50	50%
Age Group (Years)		
20-29	32	32%
30-39	35	35%
40-50	33	33%
BMI (kg/m²)		
18.5 - 22.0	42	42%
22.1 - 24.9	58	58%
Smoking Status		
Non-Smoker	100	100%
Smoker	0	0%
Physical Activity Level		

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Low	28	28%
Moderate	47	47%
High	25	25%

Table 2: Anthropometric Measurements Over Time

Parameter	Baseline (Mean ± SD)	Midpoint (6 Weeks) (Mean ± SD)	Endpoint (12 Weeks) (Mean ± SD)	F-value (ANOVA)	p-value
Weight (kg)	72.3 ± 10.2	71.0 ± 9.8	70.5 ± 9.6	4.15	0.019
BMI (kg/m²)	23.5 ± 2.7	23.1 ± 2.5	22.9 ± 2.4	5.33	0.007
Waist Circumference (cm)	82.1 ± 9.4	80.8 ± 8.7	80.1 ± 8.5	6.27	0.004

Table 3: Fasting Glucose, Insulin Levels, and HOMA-IR Over Time

Parameter	Baseline (Mean ± SD)	Midpoint (6 Weeks) (Mean ± SD)	Endpoint (12 Weeks) (Mean ± SD)	F-value (ANOVA)	p-value
Fasting Glucose (mg/dL)	95.2 ± 10.1	89.7 ± 9.8	87.5 ± 9.4	8.92	<0.001
Fasting Insulin (μU/mL)	10.5 ± 4.3	9.1 ± 4.0	8.6 ± 3.8	7.45	0.001
HOMA-IR	2.47 ± 1.1	2.01 ± 1.0	1.84 ± 0.9	9.11	<0.001

Table 4: Oral Glucose Tolerance Test (OGTT) at Baseline and Endpoint

Time Interval (minutes)	Baseline Glucose (mg/dL) (Mean ± SD)	Endpoint Glucose (mg/dL) (Mean ± SD)	F-value (ANOVA)	p-value
0	95.2 ± 10.1	87.5 ± 9.4	12.34	<0.001
30	140.3 ± 25.8	125.2 ± 23.4	11.27	<0.001
60	130.7 ± 22.1	115.4 ± 20.5	10.85	<0.001
120	105.8 ± 18.2	95.0 ± 16.7	9.65	0.002

Table 5: Insulin Sensitivity (Matsuda Index) Over Time

Parameter	Baseline (Mean ± SD)	Midpoint (6 Weeks) (Mean ± SD)	Endpoint (12 Weeks) (Mean ± SD)	F-value (ANOVA)	p-value
Matsuda Index	3.2 ± 1.1	4.1 ± 1.2	4.5 ± 1.3	13.79	<0.001

Table 6: Regression Analysis of Changes in Glucose and Insulin Response

Parameter	Baseline vs. Midpoint (Regression Coefficient, β)	Baseline vs. Endpoint (Regression Coefficient, β)	Midpoint vs. Endpoint (Regression Coefficient, β)	p-value
Fasting Glucose	-0.62 (Significant Decrease)	-0.64 (Significant Decrease)	-0.58 (Significant Decrease)	<0.001
Fasting Insulin	-0.57 (Significant Decrease)	-0.60 (Significant Decrease)	-0.54 (Moderate Decrease)	<0.001
HOMA-IR	-0.55 (Significant Decrease)	-0.56 (Significant Decrease)	-0.52 (Moderate Decrease)	<0.001
Matsuda	0.61 (Significant	0.63 (Significant	0.59 (Moderate	<0.001

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Index	Increase)	Increase)	Increase)	

Discussion

The study included 100 participants equally distributed across gender and age groups, ensuring demographic consistency. Similar demographics have been used in previous studies on intermittent fasting, such as Hutchison et al. (2019), who analyzed a cohort of 88 young women, ensuring a baseline without gender-related or age-related biases in metabolic response.[9] The inclusion of non-smokers only and standardized physical activity levels also reflects Varady et al. (2011), who found that such controls effectively reduced confounding factors, allowing more accurate observations of insulin and glucose responses to intermittent fasting.[10]

Over the 12-week study period, participants experienced a statistically significant reduction in weight, BMI, and waist circumference. The observed average weight loss (1.8 kg) and BMI reduction (23.5 to 22.9 kg/m²) in this study align with findings by Tinsley and La Bounty (2015), who reported an average 2.1 kg weight loss and similar BMI decreases in participants undergoing intermittent fasting for 10 weeks. Varady et al. (2011) also observed a significant waist circumference reduction of approximately 2 cm, consistent with our findings of a 2 cm reduction, supporting the role of intermittent fasting in decreasing central adiposity.[10,11] Both studies suggest that such reductions in waist circumference, an indicator of visceral fat, likely contribute to the enhanced insulin sensitivity seen in this study and similar studies.This study observed a decrease in fasting glucose from 95.2 mg/dL to 87.5 mg/dL and a reduction in fasting insulin from 10.5 to 8.6 μU/mL. The decrease in HOMA-IR, from 2.47 to 1.84, reflects an improvement in insulin sensitivity. In comparison, Sutton et al. (2018) observed a similar fasting glucose reduction of approximately 10 mg/dL after a 12-week intermittent fasting intervention, alongside a decrease in fasting insulin levels of about 1.8 μU/mL.[12] These findings reinforce that intermittent fasting positively impacts glucose homeostasis, potentially due to prolonged fasting periods allowing for enhanced insulin action on peripheral tissues. Similarly, Harvie et al. (2011) found a 12% reduction in HOMA-IR after eight weeks, corroborating our results and highlighting the potential of intermittent fasting in mitigating insulin resistance.[13]

The study demonstrated significant improvements in glucose tolerance over time. In the baseline OGTT, peak glucose levels reached 140.3 mg/dL at 30 minutes post-ingestion, reducing to 125.2 mg/dL at 30 minutes by the endpoint. Heilbronn et al. (2005) reported comparable reductions in postprandial glucose levels, showing an 8-12 mg/dL decrease in glucose tolerance testing among participants undergoing intermittent fasting.[14] The Matsuda Index increased significantly from 3.2 at baseline to 4.5 by the endpoint ($p<0.001$), indicating enhanced insulin sensitivity. Catenacci et al. (2016) found that intermittent fasting improved Matsuda Index values from 2.8 to 4.1, which parallels our findings and demonstrates a consistent positive impact on insulin sensitivity.[15] This improvement suggests that intermittent fasting may be particularly effective in promoting postprandial glucose clearance, further contributing to reduced insulin resistance.The regression analysis further substantiated these findings, showing strong negative correlations for fasting glucose (-0.62 to -0.58) and fasting insulin (-0.57 to -0.54) over time. These values indicate consistent reductions in both parameters, aligning with findings from Varady et al. (2011), who reported similar regression coefficients for glucose and insulin reductions, suggesting that intermittent fasting reliably promotes improved metabolic profiles over time.[10] The positive correlation for the Matsuda Index (0.61 to 0.59) aligns with Catenacci et al. (2016), who found an average increase of 0.6 over 12 weeks, further supporting intermittent fasting's role in enhancing insulin sensitivity in a sustained manner.[15]These results indicate that intermittent fasting not only improves insulin sensitivity but also enhances glucose metabolism and

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promotes positive changes in body composition. Compared to continuous calorie restriction methods, intermittent fasting has shown to be highly effective, particularly in glucose handling and insulin sensitivity improvement. This study supports intermittent fasting as a promising strategy for managing insulin resistance, potentially benefiting individuals at risk of metabolic syndrome and type 2 diabetes.

Conclusion

We concluded that intermittent fasting has significant positive effects on glucose homeostasis and insulin sensitivity. Participants showed reductions in fasting glucose, fasting insulin, and HOMA-IR values, indicating improved insulin sensitivity over the 12-week period. The increased Matsuda Index and improved OGTT results further highlight the benefits of intermittent fasting in regulating glucose levels. These findings suggest that intermittent fasting may serve as a practical and effective approach for improving metabolic health, particularly in non-diabetic individuals. Integrating intermittent fasting with other lifestyle interventions could enhance long-term health outcomes.

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