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The Effect of Intermittent Fasting and Caloric Restricted Diet on Diabetic Rats

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Abstract

The present study was aimed to investigate the effect of intermittent fasting and caloric restricted diet (RD) for 8 weeks on diabetic rats. Forty-nine adult male albino rats were divided into two main groups; the first main group was fed only on basal diet and served as negative control group and the second main group: diabetic rats were induced by a single intra-peritoneal injection of freshly prepared STZ (60 mg/kg BW) then divided into 6 subgroups: Subgroup (1) was fed only on basal diet and was served as positive cont. Subgroup (2) was fed on RD only. Subgroups (3, 4) were fed on basal diet and were deprived of food except water from 5 p.m. to 8 a.m. twice a week and every other day, respectively. Subgroups (5, 6): were fed on RD and intermittent fasting twice a week and every other day, respectively. The results indicated that RD and intermittent fasting significantly decreased the final body weight, feed intake and body weight gain % values as compared to the positive control rats. Diabetic treated rats had significant increase (p<0.05) in insulin concentration and lower glucose levels as well as an improvement in liver functions and lipid profile as compared to the positive control group. Conclusion: the findings suggest that intermittent fasting and caloric restricted diet could have a potential role in managing diabetes.

Keywords: *Diabetes- Caloric restricted- Intermittent fasting- Glucose- Lipid profile*

1. Introduction

Diabetes mellitus is reported to impact more than 100 million individuals worldwide and is one of the world's top five causes of death (Otovwe and Akpojubaro, 2020). Diabetes is a serious, long-term condition with a major impact on the lives and well-being of individuals, families, and societies worldwide (Saeedi et al., 2019). International Diabetes Federation (IDF) estimates that the global prevalence of diabetes in people aged 20-79 years is estimated at 10.5% (536.6 million) in 2021, rising to 12.2% (783.2 million) by 2045 (Sun et al., 2022)

However, current T2DM medications without lifestyle interventions lack comprehensiveness in glycemic control (Siehler et al., 2021). In light of the limitations of available antidiabetic agents, alternative treatments are highly recommended. In recent years, the dietary intervention has become a hot topic of research.

Fasting is one type of calorie restriction and has been widely practiced as a type of medical application or religious ritual. Fasting is defined as abstinence from or reduction of food, drink or both for a period typically lasting between 12 h and 3 weeks, in short-term, long-term or intermittent patterns (Lessan and Ali, 2019). Intermittent fasting is an umbrella term for various diets comprising a cycle of a period of fasting and non-fasting (Harney et al., 2019). In fact, intermittent fasting has been practiced by the Muslim population for over a thousand years in the month of Ramadan. This usually involves 12-16 h of daily fasting by abstinence of both drink and food for one month (Ahmad and Chowdhury, 2019).

Intermittent fasting (IF) is an approach that requires focusing only on fasting days to reduce energy expenditure and is potentially more straightforward to implement than calorie restriction (Anastasiou et al., 2015). It can be used as an alternative for obese individuals who have difficulty applying calorie-restricted diets for a long time (Wegman et al., 2015).

Intermittent fasting is a promising strategy among different approaches of fasting such as caloric restriction (CR) and RD. It has proved to be the most fruitful approach for its ability to cope with different diseases such as cancer, diabetes, antioxidant stress, ulcerative colitis, cardiovascular diseases, renal diseases and hypertension (Mattson et al., 2017)**.**

Numerous types of intermittent fasting, including time-restricted feeding, intermittent energy restriction, and Ramadan diurnal intermittent Ramadan fasting have recently gained considerable attention (De Cabo and Mattson, 2019), as it reportedly provokes numerous physiological changes that benefit human health. In the fasting period, cells enhance their innate defenses against oxidative and metabolic stress by activating certain pathways (Mattson et al., 2017). Clifton et al., (2021) shown that IF has a modulating function in a variety of chronic diseases, including obesity, diabetes, cardiovascular disease, multiple sclerosis, neurodegenerative diseases of the brain, and cancer**.**

Intermittent fasting appears an equivalent alternative to CR to improve health. However, few trials have considered applying meal timing during the 'fasting' day, which may be a limitation. Therefore, the aim of this work was to investigate the possible effect of intermittent fasting and caloric restricted diet on diabetic rats**.**

2. Materials And Methods

Diet: The present study was performed using standard (American Institute of Nutrition AIN- 93G purified Rodent diet) and AIN-93G vitamin and minerals were purchased from El-Gomhoria Company, Cairo, Egypt. Kits were purchased from Alkan Company for biodiagnostic Reagents, Dokki, Cairo, Egypt. Forty-nine Adult male albino rats (Sprague- Dawly strain) weighing approximately (200 ±10 g.) were purchased from Helwan Experimental Animals Farm were randomly housed in ventilated cage under controlled conditions (temperature: 22 ± 2°C, humidity: 55 ± 5%).

Study design *:*

Diabetic rats were induced by a single intra-peritoneal injection of freshly prepared STZ (60 mg/kg BW). Three days later, the level of the blood glucose was assessed and the level ≥250 mg/dl was considered as diabetes (Sarkar, et al., 1996). The experimental animals were fed on basal diet according to (Reeves et al., 1993) and were subjected to 40% caloric restriction via the basal diet.

Caloric restriction Protocol*:*

This study was carried out at the Postgraduate Lab of the faculty of Home Economic, Helwan University. Forty-nine adult male Sprague-Dawley rats were fed on standard diet for one week for adaptation. Rats were divided into two main groups; the first main group was fed only on basal and served as negative control group and the second main group: diabetic rats were induced by a single intra-peritoneal injection of freshly prepared STZ (60 mg/kg BW) then divided into 6 subgroups: Subgroup (1) was fed only on basal diet and was served as positive control group. Subgroup (2) was fed only on RD. Subgroups (3, 4) were fed on basal diet and were deprived of food except water from 5 p.m. to 8 a.m. twice a week and every other day, respectively. Subgroups (5, 6): were fed on RD and intermittent fasting twice a week and every other day, respectively .

At the end of the experimental period (8 weeks), rats were fasted over night before sacrificing, blood samples were collected into a centrifuge tube without any anticoagulant and were centrifuged to obtain serum which were stored at- 20°C until used for subsequent analysis. Body weight gain percentage (BWG %) and feed intake (FI) and Feed efficiency ratio (EFR) were calculated according to (Chapman et al., 1959).

Statistical Analysis: The obtained results were analyzed according to SPSS program Version 20 ANOVA test was used to compare results among groups and $P<0.05$ was considered to be significant (Bancroft and Stevens, 1977)

3. Results and Discussion

Table (1): Effect of intermittent fasting and caloric restricted diet on body weight status of diabetic rats

Groups	IBW (g)	FBW (G)	BWG%	FI (g/d/rat)	FER
Control (-ve)	187.00±1.47a	243.75±2.25a	30.37±1.63a	22.50	0.042±0.021a
Control (+ve)	188.00±1.22a	207.75±3.03c	10.55±2.32c	24.00	0.014±0.029c
Restricted diet (RD)	192.75±1.18a	198.00±1.29d	2.72±0.49d	20.00	0.004±0.008d
RD+ 2 day fasting	187.00±2.91a	195.75±3.70d	4.66±0.38d	20.50	0.007±0.007d
RD + fasting day/ day	187.50±1.25a	192.00±1.47d	2.40±0.46d	21.10	0.004±0.006d

Basal diet + 2 day fasting	187.75±1.65a	216.50±1.84b	15.32±0.87b	21.70	0.022±0.012b
Basal diet + fasting day / day	187.25±1.79a	215.50±1.32b	15.12±1.48b	23.70	0.020±0.018b

Data are expressed as mean ± SE

Values in each column which have different letters are significantly different at ($p<0.05$).

Table (1) display the body weight of all groups during the experimental periods. There were no significant differences of the IBW among all rats. The diabetic rats (+ve) had the lowest ($P<0.05$) final body weight, BWG% and FER while the feed intake was higher as compared to the other treated rats. Intervention with caloric restricted diet with or without intermitting fasting significantly decreased the FBW, BWG% and FER and feed intake as compared to the +ve control group. There were a significant difference ($P<0.05$) in the FBW, BWG% and FER between the diabetic groups fed RD with intermitting fasting as compared to the diabetic groups fed basal diet with intermitting fasting. There were a significant difference between the groups fed RD with 2day fasting or fasting day/day, the same trend was observed between the groups fed on basal diet. The most body weight improvement was observed at the diabetic rats fed on basal diet with 2 days fasting. The FBW, BWG% and FER of all the treated rats still significantly lowered than those of the -ve control group .

Ramadan fasting studies have shown mixed effects on health. Some studies found reduction in body weight (Kul et al., 2014) while others report minimal change (Sadeghirad et al., 2014). Similar inconsistencies are reported for the lipid profile and blood glucose levels as well. One explanation could be the confounding variables such as the fasting duration, medications, dietary habits, cultural norms and physical activity (Trepanowski and Bloomer, 2010). Other factors may include methodological differences, seasonal changes, geographical location, daylight exposures etc.

IF (4–24 weeks) induces body weight reductions of 4% to 10% in overweight individuals (Catenacci et al., 2016). The varying degree of body weight reduction depends on the dietary pattern, dietary duration, diet composition, sex, and genetic response. Although some studies have shown greater body fat reductions with IF than with CR (Alhamdan et al., 2016), the majority of these studies have shown equivalent effects on reductions in body weight and fat mass following IF or CR in overweight or obese individuals (Rynders et al., 2019).

Many studies have indicated that IF is an effective and acceptable intervention in obese subjects, including obese adolescents (Jebeile et al., 2019 and Sundfør et al., 2018), in addition, regular IF decreased fat-free mass more than CR (Roman et al., 2019). Recently, IF has appeared as an alternative dietary intervention to CR because dieters feel that IF is a more tolerable method than CR (Duregon et al., 2021).

Weight reduction may be associated with the shift from glucose to fatty acid metabolism resulting from the fasting-induced elevation in fat mobilization and utilization (De Cabo et al., 2019). The reduction in insulin, an anabolic hormone, by IF may also be responsible for the reduction in body fat mass (Zubrzycki et al., 2018).

Table (2): Effect of intermittent fasting and caloric restricted diet on blood glucose and insulin hormone of diabetic rats

Parameters / Groups	Glucose (mg/dl)	Glucose reduction (%)	Insulin	Insulin increment (%)
Control (-ve)	75.91±1.18^{g}	-	1.20±0.008^{a}	-
Control (+ve)	232.20±1.30^{a}	-	0.336±0.012^{f}	-
Restricted diet (RD)	130.73±1.57^{d}	43.69	0.620±0.017^{d}	84.52
RD+ 2 day fasting	123.59±0.88^{e}	46.77	0.736±0.016^{c}	119.04
RD + fasting day/ day	115.75±0.90^{f}	50.15	0.900±0.020^{b}	167.85
Basal diet + 2 day fasting	143.90±1.32^{b}	38.02	0.516±0.008^{e}	53.57
Basal diet + fasting day / day	136.10±1.00^{c}	41.38	0.606±0.006^{d}	80.35

Data are expressed as mean ± SE

Values in each column which have different letters are significantly different at ($p<0.05$).

Data at table (2) revealed that, serum glucose of untreated diabetic rats was significantly higher ($p<0.05$) than the negative control rats. RD significantly decreased the glucose concentrations by (43.69%) when compared to the +ve control group. Moreover, RD with different intermitting fasting (2 day fasting and fasting day/day) lowered serum glucose as compared to the rats fed on RD only by 46.77 and 50.15%, respectively. The fasting day/day model was more effective in lowering glucose than the 2-day fasting. It was clear that, the rats fed on RD with or without different intermitting fasting model had lower glucose concentration than the rats fed on basal diet with different intermitting fasting model. The lowest glucose concentration among all the tested groups was observed at the rats fed on RD with intermitting fasting day/day by.(%50.15)

Regarding to insulin hormone, the amount of insulin secretion was significantly ($P<0.05$) decreased as compared to the -ve control group. In addition, Intervention with RD improved the insulin concentration by (84.52%) when compared to the +ve control rats. It was obviously that, intervention with RD with different intermitting fasting significantly increased insulin levels as compared to the +ve group by 119.04 and 167.85, respectively. Moreover, diabetic rats fed on basal diet with different intermitting fasting increased Insulin concentration by 53.57 and 80.35%. The highest insulin concentration was observed at the group fed on RD with fasting day/day by .(%167.85)

Intermittent fasting plus early time-restricted eating provided modest benefit for postprandial glycemia in response to mixed-meal tolerance test compared with daily CR without timing advice in adults at elevated risk of type 2 diabetes after 6 months. This study adds to the growing body of evidence to indicate that meal timing and fasting advice might be influential in clinical practice (Teong et al., 2023).

IF, in any form, leads to significant weight loss and reduction in the whole body and visceral fat (Carter et al., 2018) and both weight and visceral fat gain are associated with an increased risk of T2DM (Neeland et al., 2012). Previous studies on people with T2DM have shown that IF can result in comparable weight loss and glycated haemoglobin (HbA1c) reduction as traditional dietary recommendations (Parvaresh et al., 2019).

Intermittent fasting diets have certain therapeutic effects on blood glucose and lipids in patients with metabolic syndrome and significantly improve insulin resistance (Yuan, et al., 2022). Since IF intervention, patients with T2DM have experienced improvements in glycemic parameters and partial reductions in medication intake. IF could improve patient motivation and compliance and reduce medication side effects. As no severe hypoglycemic events and other adverse events have been reported, IF can be considered a relatively safe dietary intervention for T2DM patients (CHEN et al., 2023).

Table (3): Effect of intermittent fasting and caloric restricted diet of serum lipid profile of diabetic rats Parameters

Groups / **Parameters**	**Total Cholesterol**	**Triglyceride**	**HDL-C**	**LDL-C**	**VLDL-C**
	(mg/dl)				
Control (-ve)	119.13±1.71[g]	73.53±1.37[g]	62.46±0.93[a]	41.96±1.84[g]	14.70±0.27[g]
Control (+ve)	171.20±2.73[a]	134.60±1.49[a]	25.60±0.96[e]	118.68±3.34[a]	26.92±0.29[a]
Restricted diet (RD)	143.73±1.12[d]	116.33±1.48[d]	44.93±0.81[c]	75.53±1.33[d]	23.26±0.29[d]
RD+ 2 day fasting	128.76±0.67[f]	108.60±1.15[e]	47.60±0.92[b]	66.58±0.30[e]	21.72±0.23[e]
RD + fasting day/ day	135.90±0.80[e]	98.56±1.31[f]	50.13±1.46[b]	58.92±1.99[f]	19.71±0.26[f]
Basal diet + 2 day fasting	161.00±1.19[b]	125.86±1.11[b]	36.43±0.34[d]	99.39±1.27[b]	25.17±0.22[b]
Basal diet + fasting day / day	155.90±1.05[c]	120.93±1.03[c]	39.06±0.41[d]	92.64±0.57[c]	24.18±0.20[c]

Data are expressed as mean ± SE

Values in each column which have different letters are significantly different at ($p<0.05$).

Table (3) showed the lipid profile of all groups. Significant variations were detected between the +ve control groups and the -ve control group. All the treated rats with RD or basal diet with or without intermitting fasting had lower lipid profile (TC, TG, LDL-c and VLDL-c) and higher HDL-c compared to the +ve control group. In terms with RD groups, the rats fed on RD with 2 day fasting had a greater lipid profile reduction than those of the groups treated with RD. In addition, diabetic rats fed on basal diet with 2 days fasting had lower lipid profile and greater HDL-c than the group fed on basal diet with fasting day/day. Also, the RD model was more effective in lowering lipid profile than those fed on basal diet. The highest lipid profile reduction and highest HDL-c concentration were seen at the diabetic rats fed on RD and 2 days fasting compared to the other treated rats.

Harvie et al., (2013) found that 3 months on an IF diet significantly reduced the blood lipid levels of patients with impaired glucose and lipid metabolism. In addition, Moro et al., (2016) observed lipid profile enhancement (increased HDL-c and decreased LDL-c) in a 2-month trial of IF in healthy men. The mechanisms of improving cardiovascular disease risks by IF may result from obesity control, improved lipid profiles, elevated adiponectin levels (Bhutani et al., 2010), and a suppressed inflammatory state (Fothergill et al., 2016). Additionally, increased hepatic fatty acid oxidation in the fasting state results in reduced hepatic accumulation of triglycerides, which sequentially decreases the hepatic production of VLDL and plasma levels of VLDL (Grajower and Horne, 2019).

Santos et al., (2018) have compiled data from different trials and concluded that different types of IF can increase HDL by 1–14 mg/dl, decrease LDL by 1–47 mg/ dl, decrease TC by 5–88 mg/dl and decrease TG by 3–64 mg/dl. Previously conducted trials have mentioned that intermittent fasting of 12–36 h results in a metabolic switch (Anton et al., 2018) leading to a breakdown of triglycerides into fatty acids and glycerol and conversion of fatty acids to ketone bodies in the liver (De Cabo and Mattson, 2019). During fasting, fatty acids and ketone bodies provide energy to cells and tissues (Malinowski et al., 2019). Intermittent fasting (12 h during daytime, three times per week for 6 weeks) may protect cardiovascular health by improving the lipid profile and raising the sub-optimal HDL. Intermittent fasting may be adopted as a lifestyle intervention for the prevention, management, and treatment of cardiovascular disorders (Ahmed et al., 2020).

Table (4): Effect of intermittent fasting and caloric restricted diet on serum liver functions of diabetic rats

Parameters / Groups	ALT	AST
	μ/L	
Control (-ve)	46.46±1.00[e]	32.70±1.26[e]
Control (+ve)	131.42±1.16[a]	106.50±1.337[a]
Restricted diet (RD)	113.10±0.25[c]	57.00±1.47[c]
RD+ 2 day fasting	113.10±0.75[c]	53.73±0.81[d]
RD + fasting day/ day	110.60±0.88[d]	47.73±0.81[d]
Basal diet + 2 day fasting	117.26±0.69[b]	63.76±1.49[b]
Basal diet + fasting day / day	117.20±0.63[b]	58.90±3.62[bc]

Data are expressed as mean ± SE

Values in each column which have different letters are significantly different at ($p<0.05$).

The effect of intermittent fasting and caloric restricted diet on serum liver functions of diabetic rats was shown at table (4). Injection with STZ caused a significant increase in liver functions (ALT and AST) as compared to the -ve control group. Rats fed on RD with or without intermitting fasting had lower serum ALT and AST compared to the +ve control group. Moreover, rats fed on basal diet with intermitting fasting showed reduced liver functions as compared to the +ve control group. Notably, the most common improvement in liver functions was clearly observed at the diabetic rats fed on RD with fasting day/day .

The role of fasting therapy on liver enzymes, among healthy persons was verified (Naveen et al., 2014). It was observed that excessive caloric intake, as well as food consumption throughout the day, can influence liver lipid accumulation (Koopman et al., 2014). The altered levels of liver enzymes may be associated with variations in cytokine levels and alterations in circadian rhythms of hormones as a result of Ramadan fasting (Nasiri et al., 2016)

This is partially similar to that reported by Pirmadah et al., (2020) in patients who mentioned that IF might positively affect liver function in diseased patients. It was also concluded that daily 12 h of intermittent fasting for one month significantly reduced the liver weight of mice, which is associated with enhanced liver metabolism (Jianbo et al., 2021) .

Various researchers have reported that fasting may lead to improvements in liver function, potentially indicating a reduction in liver fat accumulation or inflammation (Badran et al., 2022). Additionally, IF can affect the gut microbiota, leading to changes in bile acid metabolism, which can impact lipid metabolism and hepatic steatosis (Khan et al., 2022). Moreover, Ramadan fasting model can induce positive metabolic changes and improve alterations associated with NAFLD, including weight gain, lipid profile, liver enzymes, and hepatic steatosis (Alasmari et al., 2023).

4. Conclusion

In conclusion, the data present the evidence demonstrating the beneficial effects of restricted diet with intermitting fasting in a rat model with diabetes, suggesting that restricted diet with intermitting fasting exerts potential hypoglycemic, hepatoprotective, hypolipidemic effects.

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تأثير الصيام المتقطع والحمية منخفضة السعرات علي الفئران المصابة بالسكري

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أجريت هذه الدراسة لمعرفة تأثير الصيام المتقطع والحمية منخفضة السعرات علي الفئران المصابة بالسكري . تم تقسيم 49 فأرا وزنها حوالي (200± 10 جم) إلي مجموعتين رئيسيتين ، المجموعة الرئيسية الأولي تم تغذيتها علي نظام غذائي اساسي كمجموعة ضابطة سالبة ، المجموعة الرئيسية الثانية تم إحداث داء السكري لها عن طريق الحقن بمادةSTZ تم تغذيتها علي النظام الغذائي الأساسي وتم تقسيمها إلي ستة مجموعات فرعية علي النحو التالي : المجموعة الأولي الفرعية تم تغذيتها علي النظام الغذائي الأساسي كمجموعة ضابطة موجبة ، تم تغذية المجموعات (3,4) علي النظام الغذائي الأساسي وحرمانهم من الطعام بإستثناء الماء. والمجموعات (5,6) تم تغذيتها علي نظام الصيام المتقطع. وفي نهاية التجربة أدي الصيام المتقطع والحمية منخفضة السعرات إلي حدوث نقص في وزن الجسم النهائي ، معدل تناول الطعام بالمقارنة مع فئران المجموعة الضابطة الموجبة. سجلت الفئران المصابة بالسكر إلي زيادة معنوية ($p<0.05$)في تركيز الأنسولين وإنخفاض مستويات الجلوكوز بالإضافة إلي تحسن في وظائف الكلي وإنخفاض في مستوي الدهون .الخلاصة : تشير النتائج إلي أن الصيام المتقطع والحمية منخفضة السعرات يمكن أن يكون لديها دور فعال في علاج مرض السكري .

الكلمات المفتاحية : السكري ، الحمية منخفضة السعرات ، الصيام المتقطع ، الجلوكوز ، وظائف الدهون