

The Impact Of Intermittent Fasting Regimen On Hypertension And Cardiovascular Diseases

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Abstract

A large reduction in the high density lipoprotein level is a prognostic marker of cardiovascular disease. Intermittent fasting is a form of time restricted eating for typically 16 h fasting and 8 h eating, which discovered in recent years and shows as a new paradigm in the weight loss and the reduction of inflammation and has many long term health benefits. In this review, focusing on the effects of intermittent fasting on the cardiovascular , its benefits for diabetes mellitus type 2, lowering of blood pressure, and exploring other cardiovascular risk factors such as lipid profile and inflammation. It was investigated daily blood pressure changes monthly during fasting periods ranged six months in a cohort of 30 subjects hypertensive onmedicated. Subjects underwent an intermittent fasting program with a daily intake of ≈ 500 -600 kcal. Weight and stress scores decreased during fasting. Body weight decreased from 90 ± 1 to 75 ± 3 kg, body mass index decreased from 37.58 ± 1 to 29.66 ± 0.5 kg/m², total cholesterol decreased from 237.9 ± 1.2 to 191.1 ± 1.1 mg/dL, low density lipoprotein decreased from 80.78 ± 26.2 to 45.51 ± 0.6 mg/dL, high density lipoprotein improved from 45.6 ± 11.5 to 55 ± 5.0 mg/dL, triglycerides decreased from 227.4 ± 3.0 to 201 ± 1 mg/dL, thyroxine- T4 improved from 14.48 ± 0.5 and 3.36 ± 0.1 to 10.18 ± 0.2 and 1.82 ± 0.5 and blood pressure mean values decreased from $159 \pm 2/110 \pm 5$ to $123 \pm 1/81 \pm 1.1$ mm Hg respectively, for hypertensive medicated subjects $>160/110$ mm Hg, compared to the standard values 60 ± 1 , 25, 200, Less than 129, More than 65, 200-240, 9.0-20.0 Pmol/L, 0.15-7.0 uIU/ml. Medication was stopped in 100% of the subjects. The decrease in blood pressure was larger in subjects fasting longer. Baseline metabolic parameters, such as body mass index and glucose levels, as well as age, can be used to predict the amplitude of the blood pressure decrease during fasting.

Conclusions: Intermittent fasting for long-term tends to decrease blood pressure in subjects with elevated blood pressure values, even when subjects stopped their antihypertensive medication.

Keywords: Intermittent fasting, cardiovascular diseases, lipid profile, blood pressure.

1. Introduction

The management of high blood pressure is an important health issue because it is one of the leading risk factors for cardiovascular diseases, values $\geq 140/90$ mm Hg are defined as hypertension [1]. Genetic, environmental, and lifestyle factors contribute to the high blood pressure development, including stress, obesity, sedentary lifestyle, excess of alcohol consumption, smoking, and high salt

intake [2], also aging and insulin resistance are associated with an increase in blood pressure, hypertension increases the risk of stroke, myocardial infarction, cardiac failure, dementia, renal failure, and blindness [3]. Cardiovascular diseases are a serious problem in the world. According to World Health Organization data, 17.9 million people (third of all deaths) die every year due to cardiovascular diseases (World Health

Organization, 2019), they most often affect people over 45 years of age. The mortality rate is different in both sexes between the ages of 45–59 in men, while after the age of 60 in women [4], these differences are related to the cardio protective effect of estrogens in premenopausal women [5]. There are some factors contribute to the development of cardiovascular diseases such as age, gender, or genetic determinants, also, smoking, obesity, lack of physical activity, disorders of lipid metabolism, hypertension, diabetes, and poor diet [6]. Cardiovascular diseases treatment includes the importance of lifestyle changes of patient, taking into account pharmacotherapy [7]. Lifestyle are recommended as a first step to treat elevated blood pressure and reduces the risk of cardiovascular disease, with including 30 minutes of moderate physical exercise 5 to 7 days per week, and moderation of alcohol consumption and salt intake (<6 g/d), cessation of smoking, and stress reduction [8]. Meals should be varied and recommended to eat large amounts of vegetables, fruit, fish, and whole-grain bread, also the eating of red meat, sweetened beverages, and excessively salty foods (salt intake < 5 g daily) should be avoided [7, 9]. Also Individuals are advised to maintain a normal body mass index and waist circumference < 88 cm in women, when lifestyle modification fails, the use of antihypertensive medication is recommended [10]. Due to the growing obesity epidemic, the search for new and effective dietetic solutions aimed at reducing calories and body mass was initiated like the intermittent fasting diet, meals are consumed within a strictly defined time within a day or week, There are two basic varieties of the intermittent fasting regimen. It may be used as follow: 16/8, 18/6 and 20/4, 16:8, consisting of a 16-hour fast, and then an 8-h nutritional window, the nutritional window can be shortened to 4 hour [11], fasting regimens have become increasingly popular in the past decade, it is developed, it is defined as a abstinence from food or a reduction of total food intake for short periods of 12 to 48 hours (intermittent fasting and time-restricted eating) or longer periods of 48 hours to 21 days or more, which is defined as long-term fasting or periodic fasting, also it has been shown to be associated with important health benefits, including a

decrease in blood pressure [12-13]. Another protocol consists of a 24-hour fasting period, alternated with a 24 hours eating period for two or three times a week or caloric restriction is used for two days a week, and a regular diet for 5 days, and a consumption of about 400–600 kcal/day [14]. Intermittent fasting is the choice for a healthier lifestyle [15] and a heart healthy dietary Pattern [16]. Intermittent fasting involves use of short strict calorie restriction and led to reduction in blood pressure [13, 17]. It is an alternative diet for weight loss and glycemic control during 12 weeks. Moreover, it is a useful substitute to obese and overweight patients [18]. There is the alternate day fasting, which consists of alternating the day when the energy limit is 75%, the so-called “fast day” and “feeding day”. Intermittent fasting can be used to reduce body weight and is cardio protective [19]. Cardioprotective effects of the alternate day fasting diet are associated with a reduction of visceral fat tissue, increased adiponectin concentration, and decreased leptin and low-density lipoprotein concentration [20], in this diet, observed an increase in hunger during the day, but increase in satiety after a meal, which resulted in consumption difficulties [21]. On other hand [13, 22] studied intermittent fasting is a form of time restricted eating (typically 16 h fasting and 8 h eating), it shows as a new paradigm in the approach to weight loss and the reduction of inflammation, and has many health benefits including the cardiovascular system and the risk factors that contribute to the development of cardiovascular disease [23], atherosclerosis progression, diabetes mellitus type 2, lowering of blood pressure, lipid profile and inflammation. Also dietary patterns, such as the dietary approaches to stop hypertension and the Mediterranean diet, have been shown to improve cardiac health, current human studies suggest that this diet could reduce the risk for cardiovascular disease with improvement in weight control, hypertension, dyslipidemia, and diabetes [16]. There are studies supports the role of intermittent fasting in improving the component composition of cardiometabolic risk factors, including weight, waist circumference, fat mass, BMI, blood pressure, total cholesterol, triglycerides, fasting insulin, and insulin resistance [24]. Franziska Grundler et al., (2020) [13]

investigated daily blood pressure changes during fasting periods ranging from 4 to 41 days in a cohort of 1610 subjects, Long-term fasting tends to decrease blood pressure stepwise in subjects with elevated blood pressure values, even the subjects stopped antihypertensive medication. So, this research aimed to The impact of intermittent fasting regimen on hypertension and cardiovascular diseases, including 30 subjects who followed intermittent fasting for five days / week for six months.

2. Materials and Methods

2.1.

participants

In total, 30 subjects were included in this study, during which the subjects had to comply with intermittent fasting program, all participants gave their informed written consent. The age range was 30 to 45 years. contraindications were a BMI <16 kg/m² and/or cachexia, anorexia nervosa or eating disorder, advanced kidney, liver, or cerebrovascular insufficiency, dementia or other debilitating cognitive disease and pregnancy or lactation period [25]. Moreover, a minimal fasting length were of 5 days/ week , a blood examination was done, all participants had their baseline blood pressure measured in the morning of the first fasting day. Fasting periods ranged six months. Blood pressure of Subjects were recorded values (160/110 mm Hg). This corresponded to guidelines to classify an individual as hypertensive according to the last International Society of Hypertension practice guidelines [1]

3. Ethical Approval

The Ethics Committee of Najran University , approved the prospective observational study on March 5, 2022. The study protocol was registered on June 5, 2022, in the Clinical Trials. Written informed consent was obtained from all participants. This study was onducted in accordance with the principles of the Declaration of Helsinki.

4. Fasting Program

All subjects underwent a physical examination before initiating the fasting period, include body

weight, body mass index, overweight, blood pressure and blood glucose level. Diet of either meat or chicken, fresh vegetables and fruits was served in 2 meals. In the morning period the subjects were advised to drink 500 ml water before eat the food, then they eat the vegetables, egg or bean, cheese little salt and tea without sugar. At noon period , the subjects were advised to drink 500 ml water before eat the food, then they eat fresh vegetables, meat or chicken, in addition, 250 mL vegetable soup. During fasting, subjects were advised to drink 2 to 3 L/day of water, also drinks green tea, apple vinegar, red tea and coffee without sugar. On average, the total calorie intake was 500 to 600 kcal/day. The fasting waP accompanied by physical activity, alternating with rest. This lasted up to 5 days/week for 6 months.

5. Measurement

Clinical examinations were conducted , data, including baseline clinical information, adverse effects, and laboratory results such as low density lipoprotein, high density lipoprotein, blood glucose level and blood pressure level including systolic blood pressure and dystolic blood pressure. Blood pressure and pulse were measured by participants by digital blood pressure system at home every morning between 6:00 am and 8:00 am and at night between 7:00 pm and 9:00 pm to record blood pressure mesurments. The measurement was conducted once on the arm in sitting position after resting for 5 minutes. Body weight was measured daily by using home balance, then hight and Waist circumference was measured before and at the end of fasting using a tape measure. WC >88 cm, blood pressure $\geq 130/85$ mm Hg, fasting glucose ≥ 5.6 mmol/L or known diabetes mellitus, TG ≥ 1.7 mmol/L, and HDL-C levels <1.3 mmol/L.

6. Clinical Blood Parameters

Baseline blood samples were collected by medical assistants in the morning. Blood glucose, glycated hemoglobin, cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides, as well as sodium, were determined according to [26]. Subjects were categorized into groups that are usually associated with high blood pressure, such as diabetes mellitus, when glycated hemoglobin levels were $\geq 6.5\%$,

hyperlipidemia was when low-density lipoprotein cholesterol levels were ≥ 4.14 mmol/L, and hypertriglyceridemia was when triglyceride levels were ≥ 1.7 mmol/L.

7. Statistical analysis

Differences in blood pressure level and lipid profile levels between fasting and non-fasting state were analyzed by paired student-t test. P value below 0.05 was considered statistically significant. Baseline characteristics of volunteers participants are found in Table 1, including, age, sex, high, BW, PW WC and BMI. The baseline characteristics values were before the treatment with intermittent fasting respectively (90 ± 1 , 90 ± 2 and , 37.58 ± 1).

Table 1: Baseline characteristics of subjects randomized to the intermittent fasting intervention

Baseline characteristics, n=30	Values
Age, years	30-45
Sex	female
High (Cm)	159 ± 3
BW (Kg)	90 ± 1
PW (Kg)	60 ± 1
WC (cm)	90 ± 2
BMI (Kg/m ²)	37.58 ± 1

BW: Body weight

PW: Perfect weight

WC: Waist circumference

BMI: Body mass index

The P value is indicated for the multigroup comparisons. Values represent the mean \pm SD

8. Results and discussion

It appeared that blood pressure response to fasting was highly variable and individualized, then evaluated whether clinical parameters measured before the fasting intervention could inform on the amplitude of the BP decrease. The correlation between the predicted values and actual values in the test set was statistically significant ($P < 0.05\%$ for SBP and DBP). The present study reports blood pressure variations during intermittent fasting in a small cohort of 30 subjects (women), documenting concomitant changes in antihypertensive medication. We found that intermittent fasting affects blood pressure, leading to a normalization [27]. In this study, the blood pressure lowering effect of intermittent fasting led to the reduction of the intake of antihypertensive drugs, in addition, the ability to stop the medication. In both cases, reduction and stopping of medication, the decrease in blood pressure was maintained during the whole fasting period as well as during the period of food reintroduction [28]. Data represented table 2 showed improvement in the body weight, Waist circumference, body mass index, pre-diabetes, systolic blood pressure, diastolic blood pressure and heart rate values post the treatment with intermittent fasting respectively (75 ± 3 , 48 ± 2 , 29.66 ± 0.5 , $110/71 \pm 3.1$, 123 ± 1 , 81 ± 1.1 and 71 ± 0.3), compared to the values before the treatment (90 ± 1 , 90 ± 2 , 37.58 ± 1 , $134/90$, 150 ± 1.2 , 110 ± 1.5 and 74 ± 0.5). Intermittent fasting tends to decrease blood pressure in subjects with elevated blood pressure values according to [13].

Table 2: Effect of intermittent fasting on baseline characteristics and blood pressure in six months

Baseline characteristics, n=30	Before intermittent fasting	Post intermittent fasting	Standarded
BW Kg	90 ± 1	75 ± 3	60 ± 1
PW Kg	60 ± 1	60 ± 1	60 ± 1
WC cm	90 ± 2	48 ± 2	—
BMI Kg/m ²	37.58 ± 1	29.66 ± 0.5	25
Pre-diabetes	134/90	$110/71 \pm 3.1$	120/80
SBP mmHg	150 ± 1.2	123 ± 1	120
DBP mmHg	110 ± 1.5	81 ± 1.1	80
Heart rate (bpm)	74 ± 0.5	71 ± 0.3	Normal, no acute ischemic signs

SBP: Systolic blood pressure

DBP: Diastolic blood pressure

Data in table 3 showed the effect of intermittent fasting on lipid profil, including TC, LDL, HDL, TG and thyroxine- T4 (191.1 ± 1.1 , 45.51 ± 0.6 , 55 ± 5.0 , 201 ± 1 , 10.18 ± 0.2 and 1.82 ± 0.5) respectively, compared to the values before the treatment (237.9 ± 1.2 , 80.78 ± 26.2 , 45.6 ± 11.5 , 227.4 ± 3.0 , 14.48 ± 0.5 and 3.36 ± 0.1). From theses results, a significant improvement in the lipid profil and thyroxine- T4 post the treatment with intermittent fasting, compared to the standard values (200, Less than 129, More than 65, 200-240, 9.0-20.0 and 0.15-7.0) respectively. Intermittent fasting have a positive impact on lipid values, in a study with 60 adults who were overweight or obese, the alternative day fasting group who underwent a 75% caloric restriction every other day had a reduction in LDL and reduction in triglycerides after 12 weeks [29]. These changes could be explained by weight loss observed, fasting in Ramadan had better HDL, LDL, triglycerides, and very low-density lipoprotein levels [30]. On other hand, participants

who were obese showed improvement in HDL and LDL after 12 weeks of alternative day fasting combined with exercise [31]. According to [13] studied intermittent fasting as a heart healthy dietary pattern, and current human studies that suggest this diet could reduce the risk for cardiovascular disease with improvement in weight control, hypertension, dyslipidemia, and diabetes, also, reducing oxidative stress, optimization of circadian rhythms, and ketogenesis. The regulation and function of the thyroid during fasting for time period or intermittent fasting, the thyroid gland remains responsive during prolonged food deprivation and that its function and production of thyroid-stimulating hormone increase with fasting duration studied by [32]. Also, islamic fasting results in statistically significant changes in thyroid-stimulating hormone concentrations, islamic fasting improves quality of life scores in the domains of physical and psychological health and social interactions [33].

Table 3: Effect of intermittent fasting on lipid profil and thyroxine- T4 in six months

lipid profil and thyroxine- T4	Before intermittent fasting	Post intermittent fasting	Standared
TC mg/dL	237.9 ± 1.2	191.1 ± 1.1	200
LDL-C mg/dL	80.78 ± 26.2	45.51 ± 0.6	Less than 129
HDL-C mg/dL	45.6 ± 11.5	55 ± 5.0	More than 65
TG mg/dL	227.4 ± 3.0	201 ± 1	200-240
FT4 Pmol/L	14.48 ± 0.5	10.18 ± 0.2	9.0-20.0
TSH uIU/ml	3.36 ± 0.1	1.82 ± 0.5	0.15-7.0

TC: Total cholesterol

LDL-C: Low density lipoprotein cholesterol

HDL-C: High density lipoprotein cholesterol

TG: Triglycerides

FT4: Free thyroxine

TSH: Thyroid stimulating hormone.

9. Conclusion

In conclusion, the intermittent fasting protocol used in this study is a safe and well-tolerated

approach to normalize elevated blood pressure in subjects without antihypertensive drug intake. Intermittent fasting affects weight reduction, lifestyle changes and decreases blood pressure level, so intermittent fasting appears to be a promising nonpharmacological complementary approach in the treatment of hypertension.

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References

- (1) Unger T, Borghi C, Charchar F, Khan NA, Poulter NR, Prabhakaran D, Ramirez A, Schlaich M, Stergiou GS, Tomaszewski M. (2020). International Society of Hypertension global hypertension practice guidelines. *Hypertension*. 2020;75:1334–1357.
- (2) Nicoll R, Henein M.(2018). Caloric restriction and its effect on blood pressure, heart rate variability and arterial stiffness and dilatation: a review of the evidence. *Int J Mol Sci*. 2018;19:751.
- (3) Dorans KS, Mills KT, Liu Y, He J.(2018). Trends in prevalence and control of hypertension according to the 2017 American College of Cardiology/ American Heart Association (ACC/AHA) Guideline. *J Am Heart Assoc*. 2018;7:e008888. DOI: 10.1161/JAHA.118.008888.
- (4) Cierniak-Piotrowska, M.; Marciniak, G.; Stańczak, J. GUS, Statystyka zgonów i umieralności z powodu chorób układu krążenia, (2016). Available online: <http://bip.stat.gov.pl/organizacja-statystykipublicznej/rzadowa-rada-ludnoscowa/publikacje-rzadowej-rady-ludnoscowej/> (accessed on 1 February 2019).
- (5) Grodstein, F.; Manson, J.; Stampfer, M. (2006). Hormone therapy and coronary heart disease: The role of time since menopause and age at hormone initiation. *J. Womens Health* 2006, 15, 35–44.
- (6) Matyjaszczyk, P.; Hoffmann, K.; Bryl, W.(2011). Epidemiology of selected risk factors for cardiovascular disease. *Prz Kardiodiabet* 2011, 6, 255–262.
- (7) Jankowski, P. (2018). Principles of cardiovascular disease prophylaxis in 2018. *Kardiologia Inwazyjna* 2017, 12, 42–48.
- (8) Bakris G, Ali W, Parati G.(2019). ACC/AHA versus ESC/ESH on hypertension guidelines: JACC guideline comparison. *J Am Coll Cardiol*. 2019;73:3018–3026.
- (9) Sofi, F.; Abbate, R.; Gensini, G.F.; Casini, A.(2010). Accruing evidence on benefits of adherence to the Mediterranean diet on health: An updated systematic review and meta-analysis. *Am. J. Clin. Nutr.* 2010, 92, 1189–1196.
- (10) Whelton PK, Carey RM, Aronow WS, Casey DE, Collins KJ, Himmelfarb CD, DePalma SM, Gidding S, Jamerson KA, Jones DW,(2017). Guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/ American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2018;138:e484–e594.
- (11) Johnstone, A.(2014). Fasting for weight loss. An effective strategy or latest dieting trend? *Int. J. Obes.* 2014, 39, 727– 733.
- (12) de Cabo R, Mattson MP, (2019). Effects of intermittent fasting on health, aging, and disease. *N Engl J Med*. 2019;381:2541–2551.
- (13) Franziska Grundler, MSc; Robin Mesnage, PhD; Andreas Michalsen, MD, PhD; Françoise Wilhelmi de Toledo, MD, (2020). Blood Pressure Changes in 1610 Subjects With and Without Antihypertensive Medication During Long-Term Fasting. *Journal of the American Heart Association*. 2020;9:e018649. DOI: 10.1161/JAHA.120.018649.
- (14) Harvie, M.; Howell, A.(2017). Potential benefits and harms of intermittent energy restriction and intermittent fasting amongst obese, overweight, and normal weight subjects—A narrative review of human and animal evidence. *Behav. Sci.* 2017, 7, E4.
- (15) Kavitha Ganesan, Yacob Habbous, Senan Sultan, (2018). Intermittent Fasting: The Choice for a Healthier Lifestyle. *Cureus* 10(7): e2947. DOI 10.7759/cureus.2947.
- (16) Tiffany A. Dong, MD,a,b Pratik B. Sandesara, MD,b,c Devinder S. Dhindsa, MD,b,c

- Anurag Mehta, MD,b,c Laura C. Arneson, MD,d Allen L. Dollar, MD,c Pam R. Taub, MD,e Laurence S. Sperling, MD, (2020). Intermittent Fasting: A Heart Healthy Dietary Pattern?. *The American Journal of Medicine*, Vol 133, No 8, August 2020.
- (17) Stekovic S, Hofer SJ, Tripolt N, Aon MA, Royer P, Pein L, Stadler JT, Pendl T, Prietl B, Url J.(2019). Alternate day fasting improves physiological and molecular markers of aging in healthy, non-obese humans. *Cell Metab*. 2019;30:462–476.e465.
- (18) Carter S.; Clifton, P.M.; Keogh, J.B.(2016). The effects of intermittent compared to continuous energy restriction on glycaemic control in type 2 diabetes; a pragmatic pilot trial. *Diabetes Res. Clin. Pract.* 2016, 122, 106–112.
- (19) Barnosky, A.R.; Hoddy, K.K.; Unterman, T.G.; Varady, K.A.(2014). Intermittent fasting vs. daily calorie restriction for type 2 diabetes prevention: A review of human findings. *Transl. Res.* 2014, 164, 302–311.
- (20) Patterson, R.E.; Sears, D.D.(2017). Metabolic Effects of Intermittent Fasting. *Annu. Rev. Nutr.* 2017, 37, 371–393.
- (21) Heilbronn, L.K.; Smith, S.R.; Martin, C.K.; Anton, S.D.; Ravussin, E.(2005). Alternate-day fasting in nonobese subjects: Effects on body weight, body composition, and energy metabolism. *Am. J. Clin. Nutr.* 2005, 81, 69– 73.
- (22) Bartosz Malinowski , Klaudia Zalewska , Anna Węsierska , Maya M. Sokołowska , Maciej Socha , Grzegorz Liczner , Katarzyna Pawlak-Osińska and Michał Wiciński, (2019). Intermittent Fasting in Cardiovascular Disorders— An Overview. *Nutrients* 2019, 11, 673; doi:10.3390/nu11030673.
- (23) Callan Gavaghan, Rohan Jayasinghe, (2018). Intermittent fasting for cardiovascular disease risk factor reduction: A narrative review of current evidence. *Australasian Medical Journal* 2018;11(8):426-433.
- (24) Fan Yang, Can Liu, Xu Liu, Xiandu Pan, Xinye Li , Li Tian, Jiahao Sun , Shengjie Yang , Ran Zhao, Na An, Xinyu Yang1, Yonghong Gao and Yanwei Xing, (2021). Effect of Epidemic Intermittent Fasting on Cardiometabolic Risk Factors: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Frontiers in Nutrition* | October 2021 | Volume 8 | Article 669325.
- (25) Wilhelmi de Toledo F, Buchinger A, Burggrabe H, Hölz G, Kuhn C, Lischka E, Lischka N, Lützner H, May W, Ritzmann-Widderich M.(2013). Fasting therapy-an expert panel update of the 2002 consensus guidelines. *Forsch Komplementmed.* 2013;20:434–443.
- (26) Wilhelmi de Toledo F, Grundler F, Bergouignan A, Drinda S, Michalsen A.(2019). Safety, health improvement and well-being during a 4 to 21-day fasting period in an observational study including 1422 subjects. *PLoS One.* 2019;14:e0209353.
- (27) Reidenberg MM, (2011). Drug discontinuation effects are part of the pharmacology of a drug. *J Pharmacol Exp Ther.* 2011;339:324–32.
- (28) Li C, Ostermann T, Hardt M, Lüdtke R, Broecker-Preuss M, Dobos G, Michalsen A, (2013). Metabolic and psychological response to 7-day fasting in obese patients with and without metabolic syndrome. *Complement Med Res.* 2013;20:413–420.
- (29) Varady KA, Bhutani S, Klempel MC, Kroeger CM, (2011). Comparison of effects of diet versus exercise weight loss regimens on LDL and HDL particle size in obese adults. *Lipids Health Dis* 2011;10:119.
- (30) Nematy M, Alinezhad-Namaghi M, Rashed MM, (2012). Effects of Ramadan fasting on cardiovascular risk factors: a prospective observational study. *Nutr J* 2012;11:6.
- (31) Bhutani S, Klempel MC, Kroeger CM, Trepanowski JF, Varady KA, (2013). Alternate day fasting and endurance exercise combine to reduce body weight and favorably alter plasma lipids in obese humans. *Obesity (Silver Spring)* 2013;21:1370–9.
- (32) Bridget Martinez¹, Michael Scheibner², José G. Soñanez-Organis³, John T. Jaques⁴, Daniel E. Crocker⁵, and Rudy M. Ortiz, (2018). Increased Sensitivity of Thyroid Hormone-mediated Signaling Despite Prolonged Fasting. *Gen Comp Endocrinol.* 2017 October 01; 252: 36–47. doi:10.1016/j.ygcen.2017.07.023.
- (33) Aisha Sheikh; Minaz Mawani; Saeed Ahmed Mahar, (2018). Impact of Ramadan fasting on thyroid status and quality of life in patients with

primary hypothyroidism: A prospective cohort study from Karachi, Pakistan. *Endocrine Practice* Vol 24 No. 10 October 2018.