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Research Article

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Development of Metabolically Obese but Normal Weight (MONW) Wistar Rats by Oral Administration of Hypercaloric Emulsion

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Abstract Obesity is defined as the accumulation of adipose tissue, overweight and obesity are defined on the basis of body mass index and this is accompanied by an increased prevalence of comorbidities as type 2 diabetes, cardiovascular and metabolic disease in the population. The standard relationship between weight status and metabolic health is not applicable for some subtypes of individuals, the subtypes are known as "metabolically obese, but normal-weight", and others are the "metabolically healthy, but obese" phenotypes. Regarding the problem of obesity there are areas of progress, greater social and political awareness, development of new treatments, and an extended base of evidence for its prevention and intervention. In contrast, the prevalence of this has increased rapidly in the last two decades, largely to the lifestyle of large cities. For the study of overweight, obesity and its physiopathology consequences, in addition to clinical studies in humans, are used animal models for understand the evolution of disease and support the development of therapies, the animal models, the current animal models generate rats with phenotype metabolically obese with overweight. In this research we proposed to evaluate the effect of intragastric administration of a hypercaloric emulsion composed of fructose syrup and edible vegetable oil on development of obesity in rats, we obtained rats with phenotype metabolically healthy but obesity only in eight weeks with adiposity index of 11.5 vs 5.9 of control group and 8.3 on sham group with fructose drinking solution.

Keyword: Overweight, Obesity, Adipocity index, Metabolic disorders, Hypercaloric emulsion.

Introduction

Obesity is defined as the accumulation of adipose tissue [1], the main factor that induces obesity is the excess of carbohydrates and fats [2]. In 2008, an expert panel from the Obesity Society concluded that "the obesity is a complex condition with many causal contributors, including many factors that are largely beyond individuals" [3], [4]. Overweight and obesity are defined on the basis of body mass index (BMI), this is accompanied by an increased prevalence of comorbidities as type 2 diabetes (MD2), cardiovascular and metabolic disease in the population, included metabolic syndrome [5–8]. Around the world the obesity has increased more of double since 1980, and more than 3.4 million people die every year because of this [9],currently affects 5% of children and 12% of adults [10]. Currently, overweight and obesity is considered one of the main public health problems in the world as result of growing and development of big cities with consequent accumulation of food and sedentary life style [11]. Special importance have the abdominal adipose tissue, which is strongly predictive of metabolic health [12, 13].

Abdominal obesity is the result of the consumption of diets high in carbohydrates and fats, as well as foods with low nutritional value, coupled with lack of physical activity [10, 14].

The increase of the intraabdominal or visceral adipose tissue causes an increase in the flow of free fatty acids (FFA) towards the splanchnic circulation, while the subcutaneous tissue derivatives avoid the hepatic circulation and its consequences (increase of glucose production, lipids synthesis and secretion of prothrombotic proteins). It has also been found that the deposit of fat can be acquired in abnormally large peripheral adipocytes. The effect of adipocyte size on the risk of MD2 development seems to be independent and additive to the effect of insulin resistance [15]. Dyslipidemia in metabolic disorders is characterized by elevated TG and very low density lipoprotein (VLDL), low high density lipoprotein (HDL) and low density lipoprotein (LDL), which has been termed atherogenic lipoprotein phenotype [16]. Normal lipid metabolism includes the release of FFA from adipocytes to circulating blood, to the liver and muscle. In the liver, a part is oxidized and most are re-esterified to TG. There is a continuous transport of FFA between adipose tissue and liver; however, if the re-esterification process becomes saturated, the accumulation of TG can lead fatty liver.

The standard relationship between weight status and metabolic health is not applicable for some subtypes of individuals. The subtypes are known as "metabolically obese, but normal-weight" (MONW), and others are the "metabolically healthy, but obese" (MHO) phenotypes [4, 17]. The MONW phenotype are those who are normal weight with an abnormal metabolic status. On the other hand, the MHO phenotype is those with a normal metabolic profile who is obese [17]. As opposed to the MHO phenotype, the MONW phenotype has gained interest. These patients are not obese per BMI criteria but have a dysfunctional metabolic profile as would be typically found with obesity. Identifying potential risk factors associated with the MONW will be important to decide if health behaviors should be modified [17]. Likewise, the factors associated with the MHO will indicate effective ways to prevent obesity-related metabolic abnormalities [17]. MONW persons are a subgroup of individuals who have normal weight and body mass index (BMI), but display a cluster of obesity-related abnormalities. Although there has long been clinical recognition of this group of individuals, to our knowledge they were first described in detail in the 1980s. As described, these individuals can be young and display premature signs of insulin resistance, hyperinsulinemia, and dyslipidemia that may eventually increase their risk for the development of diabetes and cardiovascular disease [4].

Regarding the problem of obesity there are areas of progress, greater social and political awareness, development of new treatments, and an extended base of evidence for its prevention and intervention. In contrast, the prevalence of this has increased rapidly in the last two decades [18], largely to the lifestyle of large cities. Public health officials are conscious about the need to mobilize resources to combat obesity epidemic by developing more effective strategies for treating people who are obese and to prevent the development of obesity and/or obesity-related complications [4]. In this sense, for the study of overweight, obesity and its physiopathology consequences, in addition to clinical studies in humans, are used animal models for understand the evolution of disease and support the development of therapies. We propose to evaluate the effect of intragastric administration of a hypercaloric emulsion composed of fructose syrup and edible vegetable oil (1:1) on development of obesity. Therefore, the present study was designed to developed an obesity model with normal weight phenotype (MONW) with an hypercaloric emulsion designed for to emulate the consumption of fat and glucose substitutes for 8 weeks equivalent at 5 or 6 human years, [19, 20] for future researches.

Materials and Methods

Rats

In this research were used adult male Wistar rats often months of age. The rats were bred and acclimated in the vivarium. All experiments complied with the requirements and guidelines established by law respect at proper use, care, and management of laboratory animals.

Emulsion

The emulsion used was made with edible vegetable oil, the property for portion (15.2 ml) is 518 kJ of energetic content (5 g of linoleic acid, 1.1 g of linolenic acid, 5.9 g of monounsaturated fat 1.9 g of saturated fat). Also was

used fructose syrup, the fructose syrup at 80% was prepared with fructose powder alimentary grade at hot water bath. 100 ml of emulsion were prepared with 1:1 proportion (edible vegetable oil: fructose syrup at 80%), the emulsificant agent used was Tween 80 ® (0.7 ml/ 100 ml).

Treatment

Three groups of 7 rats were formed, the intact control group was administrated with pure water as drinking water and feed with standard rodent diet, with intragastric introduction of feeding needles 10 seconds but without administration. The sham group was administrated with fructose solution (30%) as drinking water and feed with standard rodent diet, with intragastric administration of emulsion vehicle (water-tween 80®, 0.007 ml tween/ml water). Emulsion group was administrated with fructose solution (30%) as drinking water and feed with standard rodent diet, with intragastric administration of emulsion (10 ml/kg). The food used was the Rodent Laboratory Chow 5001® ad livitum. The treatment was administrated by eight weeks.

Consumption of food and water

Every day was weighed the feed intake (Rat Chow 5001®) with bascule of 0.1 g precision. The consumption of water (intact control group) or fructose solution (30%, the sham group and treated group) was measured every day with probate of 2 ml precision.

Variation of weigth

The rats were weighted daily in the morning with bascule of 1.0 g precision.

Oral glucose tolerance test (OGTT)

For the glucose tolerance test, the rats were fasted for 5 h prior to test[21]. A 20% glucose solution was prepared[22],and this was administered v.o in the corresponding volume for a dose of 2.2 g/kg of weight[23].The blood sample was collected from the base of the tail at 0, 30, 60, 90 and 120 min[22] and was recorded in mg/ dl by glucometer determination[21].

Blood serum glucose and lipid profile

The animals were sacrificed by decapitation and the blood was collected in tubes without anticoagulant (tubes with red cap). The sample was centrifuged at 3000 rpm and serum separated with micropipette. The lipid profile was determined with the Selectra Junior® machine.

Adiposity index

The adiposity index was used as an indicator of obesity because it enables the precise evaluation of body fat percentage[2]. This was evaluated with intraperitoneal fat calculated (this included epididimal fat + retroperitoneal fat + visceral fat) by X-ray with densitometer HOLOGYC® model DISCOVERY, the image was analyzed with HOLOGIC´s software. The adiposity index was obtained as (intraperitoneal fat calculated/body weight) X 100[24].

Statistical analysis

Data was tested in normality and equal variances for parametric analysis, if any of this condition not existed then was realized non parametric analysis.

Results

Weekly consumption of food and water

The table 1 and 2 show that weekly food consumption and water diminished by oral administration of vehicle or emulsion and fructose solution (30%) as drinking water. The oral administration of emulsion generates the highest reduction of consumption of balanced food.

Table 1: Median food weekly consumption at grams

Week	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Control group*	20.8 ± 1.7	21.9 ± 3.9	24.7 ± 2.6	24.0 ± 2.0	25.7 ± 2.4	24.9 ± 1.5	25.2 ± 0.7	24.9 ± 2.0
Sham group*	14.0 ± 1.9	12.1 ± 1.2	10.1 ± 1.6	9.1 ± 4.0	10.5 ± 2.5	10.1 ± 2.8	10.8 ± 2.9	11.5 ± 2.4
Emulsion group*	7.3 ± 1.5	7.6 ± 1.7	6.3 ± 1.1	6.4 ± 1.0	7.5 ± 1.2	6.9 ± 0.9	7.7 ± 1.2	6.5 ± 0.6

Groups with n=7. *p<0.05 by ANOVA for repeated measures with Post-Hoc test of Holme-Sidak.

Table 2: Median weekly water consumption at ml

Week	1	2	3	4	5	6	7	8
Control group*	39.7 ± 7.7	45.0 ± 6.2	47.0 ± 5.3	49.8 ± 5.2	51.2 ± 3.9	54.2 ± 5.0	52.9 ± 3.2	51.7 ± 1.9
Sham group*	30.1 ± 7.9	43.4 ± 7.7	39.9 ± 3.6	39.0±13.8	44.4 ± 5.9	44.3 ± 5.5	45.1 ± 7.5	45.2 ± 7.5
Emulsion group*	21.9 ± 5.9	29.5 ± 6.0	24.4 ± 7.1	23.4 ± 5.6	28.1 ± 4.6	28.1+ 5.8	28.1 ± 5.3	26.3 ± 4.4

Groups with n=7.*p<0.05 by ANOVA for repeated measures with Post-Hoc test of Holme-Sidak.

Variation of weight

The figure 1 shows the effect of oral administration of emulsion with fructose solution (30%) and fructose solution (with oral administration of emulsion vehicle) on percentage of variation of weight. Both groups have a percentage weight reduction compared with intact control group, but without differences between them.

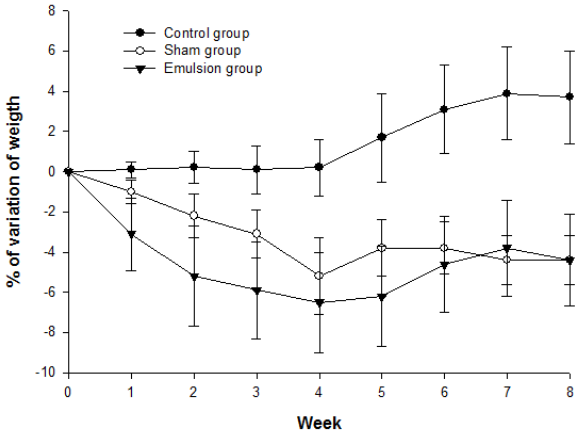


Figure 1. Percentage of variation of weight for week (median ± standard error): Control group ( ); Sham group (fructose solution at 30%) in drinking water ( ); emulsion group (oral administration of emulsion)* ( ). ANOVA for repeated measure. *p<0.05 with respect control group, Holm-Sidak post-hoc test*

Oral glucose tolerance test (OGTT)

The figure 2 shows the results of OGTT, the fructose solution (30%) as drinking water increased the blood glucose in this test, this effect was greater with oral administration of emulsion. The results show a tendency to increase glucose in blood on this test but without significant difference in the evaluated time.

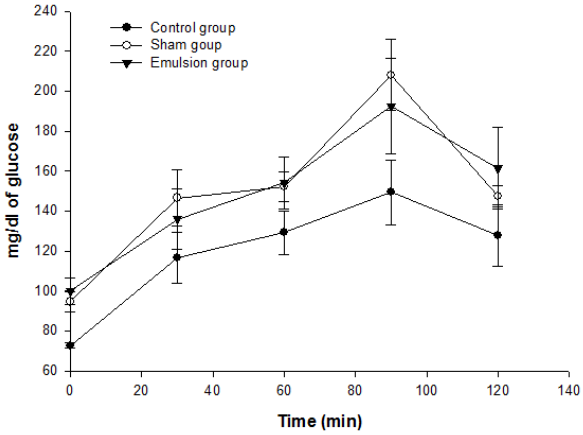


Figure 2: Oral glucose tolerance test (median ± standard error): Control group ( ); group of Fructose 30% in drinking water ( ); emulsion group ( ).

Lipid profile and glucose

The table 3 shows the blood serum glucose and lipid profile (cholesterol, triglycerides and HDL cholesterol). Glucose, Cholesterol and HDL cholesterol no present statistical differences but sham group (fructose solution 30% as drinking water) have statistical differences in triglycerides values. The emulsion group no present differences on glucose and lipid profile with control group.

Table 3: Blood serum glucose, and lipid profile

Groups	**Glucose (mg/dl) Mean ± Stdesv**	**Cholesterol (mg/dl) Mean± Stdesv**	**Triglycerides (mg/dl) Mean± Stdesv**	**HDL (mg/dl) Mean± Stdesv**
Control group	136.1 + 22.0	53.8± 5.3	71.5± 23.8	21.0± 2.0
Sham group	139.7± 7.3	61.6± 6.6	130.5 ± 28.6*	24.4± 3.4
Emulsion group	156.0± 60.1	60.1± 5.6	88.0± 57.4	21.4± 2.8

Groups with n=7. *p<0.05 vs control group by ANOVA with Post-Hoc test of SNK.

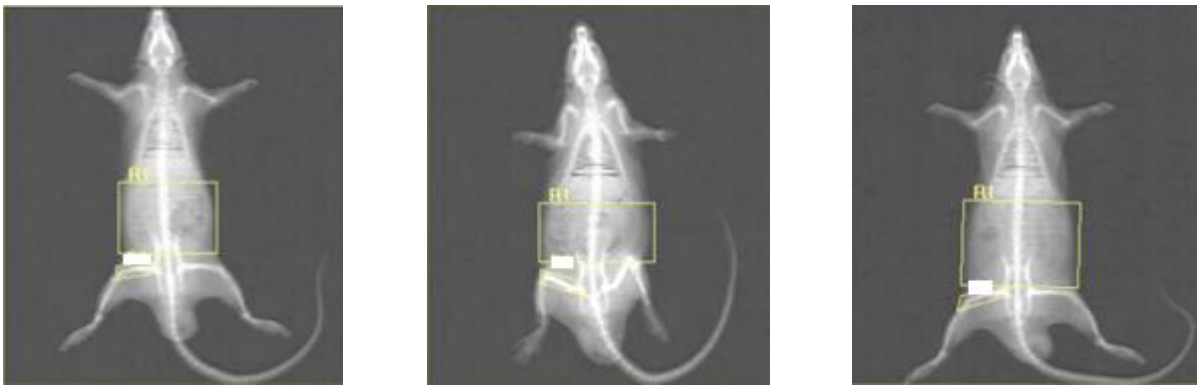
Abdominal adipose tissue and adiposity index

The table 4 shows the percentage of visceral fat calculated by X-ray (figure 3) and adiposity index. The percentage of visceral fat presented statistical difference the sham group and emulsion group with respect at control group but no have differences between them. On adiposity index the sham group and emulsion group present statistical difference with respect to control group and between them.

Table 4: Visceral fat and body mass index

Group	**Weight (g)**	**Height (cm)**	**Mean % Fat**	**BMI**	**Adiposity index**
Control	493.0	25.6	20.7±3.3	1.9	5.9(±1.4)*
Sham	571.0	25.3	30.8±1.1*	2.3	8.3(±0.4)*
Emulsion	523.4	24.9	36.3±6.6*	2.1	11.5(±2.5)*

The records are reported in mean. Groups with n=5. *p<0.05 vs control group by ANOVA with Post-Hoc test of SNK.



A B C

Figure 3: Estimation of visceral fat by X-Ray with densitometer HOLOGYC® model DISCOVERY. A) Control group; B) Sham group; C) Emulsion group.

Discussion

The consumption of feed (table 1) and water (table 2) of control group is compeered with the consumption reported by Francisqueti et al 2017 with rats of 10 weeks of age with 6, 12 and 24 weeks of feeding of an intact control group, and the consumption of our sham group (fructose solution 30% as drinking water and introduction of feeding

needles (10 seconds) without oral administration of emulsion) is compared with the group administered of fructose solution at 10% of these research [2]. The group with oral administration of emulsion take around a third rations of feed and a half of fructose solution (30%) as drinking water with respect to control group.

The current foods or supplements administered for to induce overweight or obesity in rats or mice are glucose or substitutes of glucose (naturals or artificial) diluted in drinking water (5 to 20% in general for 16 or more weeks), also be used special food with elevated caloric content of varied composition of lipids and carbohydrates [2, 6, 25–28] this treatment increased weight, body mass index and visceral fat with increase in triglycerides, cholesterol and glucose serum, that is, they generate a models of obesity with metabolic disorders and elevated weight (MUO animal model). The treatment with emulsion, evaluated in this work, generate a loss weight light (figure 1) compared with others treatments reported, the triglycerides not changes significantly with respect to control group but increased the fatty tissue, the sham group increased triglycerides concentration in compare to control and emulsion groups with increased fatty tissue between control group and emulsion group, this results suggest that differentiation of adipocytes is increased with the emulsion. The cholesterol and HDL of emulsion group are more nearly at control group values compare with sham group, the glucose no have significantly difference but have a tendency to increase inclusive more than register in sham group (table 3), in this sense, on the OGTT, the emulsion group present more intolerance to glucose (figure 2). These results are complemented with BMI with 1.9 in control group versus 2.1 to emulsion group and 2.3 in sham group (table 4). Nevertheless, adiposity index in emulsion group increase almost double with respect to control group ($p>0.05$), inclusive more than sham group (table 4, figure 3).

Although there are different recognized obesity phenotypes, for the MHO and MONW phenotypes there are no established criteria to define them. However, the study and understanding of its causes are important given that these subgroups represent more than 20% of the obese population, and understanding their causes will allow developing appropriate therapies for the treatment of obesity and for the timely diagnosis of the development of this [3, 4, 17, 29, 30]. Then, this treatment can be to use to generate a model of MONW Wistar rats, with this treatment the rats have accumulation of adipose tissue increased adiposity index, but no have increased of weight and BMI. The triglycerides, cholesterol and HDLc comparable with intact group.

Conclusion

The oral administration of emulsion (edible vegetable oil: fructose syrup at 80%, 1:1) induce obesity without increased corporal weight phenotype (MONW), with normal body mass index and lipid profile (triglycerides, cholesterol and HDL cholesterol), but increased visceral fat and with this the adiposity index. Then, this emulsion can to induce MONW phenotype animal model for future researches in design of therapies and treatments for these patients.

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References

1. E. Smith, P. Hay, L. Campbell, and J. N. Trollor, “A review of the association between obesity and cognitive function across the lifespan: Implications for novel approaches to prevention and treatment,” *Obes. Rev.*, vol. 12, no. 9, pp. 740–755, 2011.
2. F. V. Francisqueti, A. F. Nascimento, I. O. Minatel, M. C. Dias, R. D. A. M. Luvizotto, C. Berchieri-Ronchi, A. L. A. Ferreira, and C. R. Corrêa, “Metabolic syndrome and inflammation in adipose tissue occur at different times in animals submitted to a high-sugar/fat diet,” *J. Nutr. Sci.*, pp. 1–8, 2017.
3. J. Upadhyay, O. Farr, N. Perakakis, W. Ghaly, and C. Mantzoros, “Obesity as a Disease,” *Med. Clin. North Am.*, vol. 102, no. 1, pp. 13–33, 2018.
4. A. D. Karelis, D. H. St-Pierre, F. Conus, R. Rabasa-Lhoret, and E. T. Poehlman, “Metabolic and body composition factors in subgroups of obesity: What do we know?,” *J. Clin. Endocrinol. Metab.*, vol. 89, no.

6, pp. 2569–2575, 2004.

5. Y. C. Wang, K. McPherson, T. Marsh, S. L. Gortmaker, and M. Brown, "Health and economic burden of the projected obesity trends in the USA and the UK," *Lancet*, vol. 378, no. 9793, pp. 815–825, 2011.
6. H. A. Paula Neto, P. Ausina, L. S. Gomez, J. G. B. Leandro, P. Zancan, and M. Sola-Penna, "Effects of food additives on immune cells as contributors to body weight gain and immune-mediated metabolic dysregulation," *Front. Immunol.*, vol. 8, no. NOV, pp. 1–11, 2017.
7. B. G. Nordestgaard, T. M. Palmer, M. Benn, J. Zacho, A. Tybjærg-Hansen, G. D. Smith, and N. J. Timpson, "The effect of elevated body mass index on ischemic heart disease risk: Causal estimates from a mendelian randomisation approach," *PLoS Med.*, vol. 9, no. 5, 2012.
8. S. MacMahon, C. Baigent, S. Duffy, A. Rodgers, S. Tominaga, L. Chambless, G. De Backer, D. De Bacquer, M. Kornitzer, P. Whincup, S. G. Wannamethee, R. Morris, N. Wald, J. Morris, M. Law, M. Knuiman, H. Bartholomew, G. Davey Smith, P. Sweetnam, P. Elwood, J. Yarnell, R. Kronmal, D. Kromhout, S. Sutherland, J. Keil, G. Jensen, P. Schnohr, C. Hames, A. Tyroler, A. Aromaa, P. Knekt, A. Reunanen, J. Tuomilehto, P. Jousilahti, E. Vartiainen, P. Puska, T. Kuznetsova, T. Richart, J. Staessen, L. Thijs, T. Jørgensen, T. Thomsen, D. Sharp, J. D. Curb, N. Qizilbash, H. Iso, S. Sato, A. Kitamura, Y. Naito, A. Benetos, L. Guize, U. Goldbourt, M. Tomita, Y. Nishimoto, T. Murayama, M. Criqui, C. Davis, C. Hart, G. Davey Smith, D. Hole, C. Gillis, D. Jacobs, H. Blackburn, R. Luepker, J. Neaton, L. Eberly, C. Cox, D. Levy, R. D'Agostino, H. Silbershatz, A. Tverdal, R. Selmer, T. Meade, K. Garrow, J. Cooper, F. Speizer, M. Stampfer, A. Menotti, A. Spagnolo, I. Tsuji, Y. Imai, T. Ohkubo, S. Hisamichi, L. Haheim, I. Holme, I. Hjermann, P. Leren, P. Ducimetiere, J. Empana, K. Jamrozik, R. Broadhurst, G. Assmann, H. Schulte, C. Bengtsson, C. Björkelund, L. Lissner, P. Sorlie, M. Garcia-Palmieri, E. Barrett-Connor, M. Criqui, R. Langer, C. Hart, G. Davey Smith, D. Hole, K. Nakachi, K. Imai, X. Fang, S. Li, R. Buzina, A. Nissinen, C. Aravanis, A. Dontas, A. Kafatos, A. Menotti, H. Adachi, H. Toshima, T. Imaizumi, D. Kromhout, S. Nedeljkovic, M. Ostojic, Z. Chen, H. Tunstall-Pedoe, T. Nakayama, N. Yoshiike, T. Yokoyama, C. Date, H. Tanaka, J. Keller, K. Bonaa, E. Arnesen, H. Tunstall-Pedoe, E. Rimm, M. Gaziano, J. E. Buring, C. Hennekens, S. Törnberg, J. Carstensen, M. Shipley, D. Leon, M. Marmot, R. Clarke, R. Collins, J. Emberson, J. Halsey, S. Lewington, A. Palmer, S. Parish, R. Peto, P. Sherliker, and G. Whitlock, "Body-mass index and cause-specific mortality in 900 000 adults: Collaborative analyses of 57 prospective studies," *Lancet*, vol. 373, no. 9669, pp. 1083–1096, 2009.
9. K. Bowden-Davies, J. Connolly, P. Burghardt, L. G. Koch, S. L. Britton, and J. G. Burniston, "Label-free profiling of white adipose tissue of rats exhibiting high or low levels of intrinsic exercise capacity.," *Proteomics*, vol. 15, no. 13, pp. 2342–2349, Jul. 2015.
10. C. T. Dourish and P. G. Clifton, "Multidisciplinary approaches to the study of eating disorders and obesity: Recent progress in research and development and future prospects," *J. Psychopharmacol.*, vol. 31, no. 11, pp. 1383–1387, 2017.
11. S. J. Wimalawansa, "Stigma of obesity: A major barrier to overcome," *J. Clin. Transl. Endocrinol.*, vol. 1, no. 3, pp. 73–76, 2014.
12. C. A. Emdin, A. V. Khera, P. Natarajan, D. Klarin, S. M. Zekavat, A. J. Hsiao, and S. Kathiresan, "Genetic Association of Waist-to-Hip Ratio With Cardiometabolic Traits, Type 2 Diabetes, and Coronary Heart Disease," *Jama*, vol. 317, no. 6, p. 626, 2017.
13. G. R. Keele, J. W. Prokop, H. He, K. Holl, J. Littrell, A. Deal, S. Francic, L. Cui, D. M. Gatti, K. W. Broman, M. Tschannen, S.-W. Tsaih, M. Zagloul, Y. Kim, B. Baur, J. Fox, M. Robinson, S. Levy, M. J. Flister, R. Mott, W. Valdar, and L. C. Solberg Woods, "Genetic Fine-Mapping and Identification of Candidate Genes and Variants for Adiposity Traits in Outbred Rats," *Obesity*, vol. 00, no. 00, pp. 1–10, 2017.
14. J. Kaur, "A comprehensive review on metabolic syndrome.," *Cardiol. Res. Pract.*, vol. 2014, p. 943162, 2014.
15. C. Weyer, J. E. Foley, C. Bogardus, P. A. Tataranni, and R. E. Pratley, "Enlarged subcutaneous abdominal

adipocyte size, but not obesity itself, predicts type II diabetes independent of insulin resistance.," *Diabetologia*, vol. 43, no. 12, pp. 1498–1506, Dec. 2000.

16. C. Day, "Metabolic syndrome, or What you will: definitions and epidemiology.," *Diabetes Vasc. Dis. Res.*, vol. 4, no. 1, pp. 32–38, Mar. 2007.
17. K. Lee, "Metabolically obese but normal weight (MONW) and metabolically healthy but obese (MHO) phenotypes in Koreans: Characteristics and health behaviors," *Asia Pac. J. Clin. Nutr.*, vol. 18, no. 2, pp. 280–284, 2009.
18. R. F. Kushner and S. Kahan, "Introduction: The State of Obesity in 2017," *Med. Clin. North Am.*, vol. 102, no. 1, pp. 1–11, 2018.
19. N. Adami ANDREOLLO, E. Freitas dos SANTOS, M. Rachel ARAÚJO, L. Roberto LOPES, and N. Adami Andreollo, "Rat's age versus human's age: what is the relationship?," *ABCD Arq Bras Cir Dig*, vol. 25, no. 1, pp. 49–51, 2012.
20. P. Sengupta, "The Laboratory Rat: Relating Its Age With Human's.," *Int. J. Prev. Med.*, vol. 4, no. 6, pp. 624–630, Jun. 2013.
21. V. W. Dolinsky, C. F. Rueda-Clausen, J. S. Morton, S. T. Davidge, and J. R. B. Dyck, "Continued postnatal administration of resveratrol prevents diet-induced metabolic syndrome in rat offspring born growth restricted," *Diabetes*, vol. 60, no. 9, pp. 2274–2284, 2011.
22. Y. Goto, M. Kakizaki, and N. Masaki, "Production of spontaneous diabetic rats by repetition of selective breeding.," *Tohoku J. Exp. Med.*, vol. 119, no. 1, pp. 85–90, 1976.
23. S. Andrikopoulos, A. R. Blair, N. Deluca, B. C. Fam, and J. Proietto, "Evaluating the glucose tolerance test in mice," pp. 1323–1332, 2008.
24. A. J. T. Ferron, B. B. Jacobsen, P. G. Sant'Ana, D. H. S. De Campos, L. C. De Tomasi, R. D. A. M. Luvizotto, A. C. Cicogna, A. S. Leopoldo, and A. P. Lima-Leopoldo, "Cardiac dysfunction induced by obesity is not related to β-adrenergic system impairment at the receptor-signalling pathway," *PLoS One*, vol. 10, no. 9, pp. 1–18, 2015.
25. D. P. Cardinali, P. A. Scacchi Bernasconi, R. Reynoso, C. F. Reyes Toso, and P. Scacchi, "Melatonin may curtail the metabolic syndrome: Studies on initial and fully established fructose-induced metabolic syndrome in rats," *Int. J. Mol. Sci.*, vol. 14, no. 2, pp. 2502–2514, 2013.
26. A. El Midaoui, Y. Haddad, Y. Filali-Zegzouti, and R. Couture, "Argan Oil as an Effective Nutri-Therapeutic Agent in Metabolic Syndrome: A Preclinical Study," *Int. J. Mol. Sci.*, vol. 18, no. 12, p. 2492, 2017.
27. S. Samane, R. Christon, L. Dombrowski, S. Turcotte, Z. Charrouf, C. Lavigne, E. Levy, H. Bachelard, H. Amarouch, A. Marette, and P. S. Haddad, "Fish oil and argan oil intake differently modulate insulin resistance and glucose intolerance in a rat model of dietary-induced obesity," *Metabolism.*, vol. 58, no. 7, pp. 909–919, 2009.
28. M. Pearlman, J. Obert, and L. Casey, "The Association Between Artificial Sweeteners and Obesity," *Curr. Gastroenterol. Rep.*, vol. 19, no. 12, p. 64, 2017.
29. S. Velho, F. Paccaud, G. Waeber, P. Vollenweider, and P. Marques-Vidal, "Metabolically healthy obesity: Different prevalences using different criteria," *Eur. J. Clin. Nutr.*, vol. 64, no. 10, pp. 1043–1051, 2010.
30. S. L. Appleton, C. J. Seaborn, R. Visvanathan, C. L. Hill, T. K. Gill, A. W. Taylor, and R. J. Adams, "Diabetes and cardiovascular disease outcomes in the metabolically healthy obese phenotype: A cohort study," *Diabetes Care*, vol. 36, no. 8, pp. 2388–2394, 2013.