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THEMES:

- Cellular and molecular biology of brown, beige and white adipocytes
- Adipose-targeted Pharmacology
- Adipose tissue development
- Hormonal and nervous control of the adipose tissue
- Overweight, obesity, type 2 diabetes, cardiometabolic and other diseases

Abstracts submission: maximum 300 words, ends on March 25th

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REGULATION OF HORMONE-SENSITIVE LIPASE (HSL) BY HIGH-FAT DIET AND ARSENIC IN VISCERAL AND SUBCUTANEOUS ADIPOSE TISSUE IN MICE

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Lipolysis, the hydrolysis of triglycerides into three fatty acids and one molecule of glycerol, is one of the main functions of white adipose tissue and is impaired in obesity. The proper activation of hormone-sensitive lipase (HSL) is crucial for stimulated Lipolysis during fasting. Environmental factors like high-fat diet (HFD) and metabolism-disrupting chemicals, like arsenic, play an important role in adipose tissue dysfunctionality. However, little is known about how arsenic contributes to Lipolysis impairment in combination with HFD. Thus, C57BL/6 male mice fed control low-fat diet (LFD) or HFD were exposed to arsenic (100 µg/L) in drinking water for 8 weeks. Fasting glycerol, a lipolysis marker, decreased in mice fed HFD and this was more evident in combination with arsenic exposure. To identify the adipose tissue pads responsible of these changes, HSL mRNA, total HSL, and HSL phosphorylated at Ser660 (activation site) and Ser565 (inacti-

vation site) were measured in retroperitoneal and epididymal visceral adipose tissue (rVAT and eVAT, respectively) and in subcutaneous adipose tissue (SAT). Of the three adipose tissue pads, SAT had the lowest HSL amount. In rVAT and SAT, the phosphorylation in the activation site was decreased 50% only in mice fed HFD and exposed to arsenic simultaneously. However, SAT had half of the amount of pHSL660 in mice fed the control LFD. In eVAT, the phosphorylation in the activation site was decreased 60% by HFD and was more evident in combination with arsenic, lowering an extra 15%. When considering both HSL phosphorylation sites together, the ratio of the levels of phosphorylation at the activation and inhibition sites indicates a reduction of HSL activity by 50% only in rVAT of mice fed HFD and exposed to arsenic simultaneously. In summary, arsenic impairs stimulated lipolysis mainly in rVAT when mice are fed HFD.

ANGIOTENSIN 1-7 AS AN INDUCER OF THE BROWNING CAPACITY OF WHITE ADIPOSE TISSUE

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Angiotensin-(1-7)[Ang-(1-7)], a component of the renin angiotensin system is a vasodilator that exerts its effects particularly via Mas receptor. The antihypertensive drugs that inhibit the Angiotensin Converting Enzyme, such as captopril, increase Ang-(1-7) serum concentrations and have been associated with a reduction or prevention of weight gain in humans and animal models. The discovery of Mas receptor in white adipose tissue (WAT) suggests an additional role of this peptide. It is unknown if Captopril or Ang-(1-7) can activate the differentiation of beige adipocytes, a process called browning/beiging and partly explain the prevention of weight gain. Beige adipocytes are thermogenic cells that express uncoupling protein 1 (UCP1), have a higher mitochondria abundance and are associated to an increase in energy expenditure. *In vitro*

experiments in adipocytes showed that a treatment with Captopril or Ang-(1-7) induced the expression of thermogenic genes and mitochondrial respiration. On the other hand, *in vivo* experiments showed that an infusion of Ang-(1-7) increases energy expenditure and induces the mRNA expression of *Ucp1* and some beige markers in the inguinal white adipose tissue (iWAT) from Mas^{+/+} mice, effects that were abolished in Mas^{-/-} mice. The lack of Mas receptor increased body weight gain and decreased cold resistance whereas rats overexpressing Ang-(1-7) showed the opposite effects. These data indicate that Ang-(1-7) is a new factor that induces browning/beiging of iWAT through Mas receptor and has the therapeutic potential to induce thermogenesis.

ADIPOSE TISSUE REMODELING IN OBESITY

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Obesity is a chronic disease, affecting 32% of adults in Mexico. Obesity increases the risk to develop type 2 diabetes, dyslipidemias, and hypertension, representing the second cause of clinical visits in Mexico. Obesity is defined as an excessive increase of adipose tissue. The excess of fatty acids provokes the adipocytes to become hypertrophic. This adipocytes expansion provokes an increment in hypoxia, inflammation and an inadequate vascularization on the adipose tissue, leading to a reduction of its functionality. In addition, the reduction of vascularization (angiogenesis) in adipose tissue contrib-

uted to weight loss, reducing fat mass and food intake. Also, glucose homeostasis was ameliorated and triglycerides were decreased. Adipose remodeling, defined by angiogenesis, hypoxia and inflammation, has recently been suggested to contribute to metabolic modifications, causing susceptibility to obesity. The comparison between animals prone to obesity and resistant to obesity demonstrated that adipose remodeling was higher in prone animals. These findings suggested a mechanism that might contribute to develop obesity.

SEXUAL DIMORPHISM: A FACTOR IN THE INSULIN RESISTANCE MECHANISM IN METABOLIC SYNDROME MODEL

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Metabolic syndrome (MS) is a cluster of metabolic signs that increases the risk to develop type 2 diabetes mellitus and cardiovascular disease. Metabolic syndrome includes the next signs: central obesity, insulin resistance, impaired fasting glucose, hypertension, and dyslipidemia (hypertriglyceridemia and low HDL). Although it has been proposed that some of these signs are different between female and male, the insulin resistance mechanisms in metabolic syndrome are unknown. Thus, the objective of this work was to analyze the insulin signaling pathway in adipose tissue comparing female and male in a metabolic syndrome model in rats. We used Wistar female and male rats (250-280 g), which were fed with standard diet and 20% of sucrose in drinking water (treated group) or plain water (control group) during 24 weeks. After this time, both female and male treated rats developed MS with central obesity, hyperinsulinemia, insulin resistance, high triglycerides in

plasma. Furthermore, male treated rats developed hypertension and hyperglycemia. We studied total and phosphorylated AKT and P70S6K1 (S6K1) proteins in peripancreatic (PAT) and gonadal (GAT) adipose tissue. According to the results, phosphorylated AKT1 (S473) protein increased in peripancreatic adipose tissue of both female and male treated animals, while p-S6K1 diminished in male treated and there were no differences in female rats. In gonadal adipose tissue p-AKT1 and p-S6K1 proteins didn't change between treated and control male rats. While in the female p-AKT1 diminished in treated in comparison with control rats, without changes in the p-S6K protein. Our results showed that MS impaired the insulin signaling pathway and these changes are different between female and male rats.

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THE COGNITIVE ADIPOBIOLOGY: A GOLD MINE TO BE UNFOLDED

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The present lecture dealing with cognitive adipobiology (cognitive adiposcience), focusing on the pathogenesis of Alzheimer's disease. Although the human brain is nearly 50 percent lipids, the brain is the only organ which does not contain adipose tissue, except that located at the parasellar region. The brain is a *bona fide* organ mediating cognitive processes. These require collaboration with other organs, adipose tissue being an example of such mutuality. Adipokines are signaling proteins secreted from adipose cells which influence other tissues including the brain. These interactions could be disrupted in the setting of obesity. Early stage adipose accumulation is crucial for a healing process, a sustained long-lasting phase may trigger pathogenic changes including cardiometabolic and neurodegenerative (neurometabolic) diseases. The adipose tissue and the brain are both reciprocally and homeostatically regulated. A healthy adipose tissue is essential for both a healthy metabolism and a healthy brain. Today, adipose tissue is increasingly "getting nervous" secreting NGF, BDNF, meteo-

roin (Metrn) and other neurotrophic factors, also neuropeptides. Metaphorically, adipose tissue is increasing dramatically its intelligence quotient (IQ). We have even proposed that this fascinating tissue might function as a third brain, as well as the gut is commonly considered a second brain. When the adipose tissue gets sick, secondary to inflammatory cell infiltration, its dysbalanced endocrine activity represents a risk factor for cardiometabolic and neurometabolic diseases. The inflamed adipose tissue is a malfunctioning endocrine organ which may infect the brain with amyloid precursor peptide (APP), β -amyloid peptide, presenilin and other neurodegenerative substances, leading to Alzheimer disease. In a similar vein, high fat diet fed mice demonstrated a significant increase in APP expression and a decrease in the number of dendritic spines in brain neurons. In a nutshell, the early detection of brain-targeting alzheimerogenic adipokines and the identification of novel adipose-brain mechanisms may represent a gold mine to indeed be unfolded.

INFLAMMATORY MARKERS IN THE SERUM OF PRE-PUBERTAL CHILDREN WITH DOWN SYNDROME

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Down's Syndrome (DS), also known as trisomy 21 for the presence of an extra copy of the chromosome 21 that leads to a set of cognitive and physical symptoms, is one of the most common chromosomal disorder occurring in about 1 in 800 newborns world-wide. Although DS individuals are mostly perceived as characterized by some distinct physical features, cognitive disabilities and cardiac defects, they also show important deregulations of metabolic and immune functions. In this study, we evaluated serum levels of nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) and some markers of oxidative stress in patients with DS since NGF and BDNF are known to play subtle roles in the regulation of oxidative, cardiometabolic and immune physiological related events [1–4]. The pre-pubertal sample population consisted of 5 male children and 4 female children diagnosed by both a pediatric geneticist and a molecular analysis. Six pre-pubertal healthy baby-girls and 6 pre-pubertal healthy baby-boys were included in the study as controls. Venous blood samples were collected and NGF and BDNF levels were measured by ELISA assay. The mean NGF serum levels of the pre-pubertal DS patients were no significantly different compared to the controls. However, BDNF serum levels were significant higher in DS subjects compared to controls. Oxidative stress was analyzed as free oxygen radicals defense (FORD) and free oxygen radicals test (FORT) in association with a panel of cytokines whose expression levels are strongly influenced by

NGF/BDNF. Data show that in Down children serum Interleukin (IL)-1 β , IL-2, IL-6 and IL-12 are significantly reduced. Our study suggests a potential role of BDNF/NGF pathway as diagnostic marker of immune, metabolic and central nervous systems trophic disconnections in pre-pubertal Down children.

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ADIPOETHICS

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Obesity is a condition that can be recognized on sight by anybody with no medical training, yet characterizing it precisely has proven surprisingly difficult. All the proposed ways to measure obesity are plagued by methodological problems which make statistical connections with other conditions shaky. Exploring some of these methodological intricacies unveils several problems about the ways we establish what is normal, and therefore what count as being overweight. Ethical considerations about the way in which socially established notions of desirability impact what we consider normal, reveal the need to find a notion of normalcy that is independent of social conventions. Under an intuitively attractive biomedical definition of health and disease, obesity's characterization is

found to be as elusive as with purely statistical or social criteria of normalcy. This result, coupled with moral considerations about the limits to possible measures to fight the obesity epidemic, requires us to question the advisability of treating obesity at all. Moral considerations of what constitutes the good for us, allow us to understand the proper role of medicine, beyond the treatment of disease, understood from the biomedical point of view. These same considerations support the idea that obesity should indeed be treated even if its status as a disease is suspect. Finally, I contend that the awareness of the moral impact of obesity on people's lives, should be a crucial element in the efforts to effect the behavioral changes needed for patients to successfully fight obesity.

FLUVOXAMINE'S MECHANISTIC ROLE IN HFD INDUCED TISSUE DYSFUNCTIONS THROUGH PPAR- γ , ADENOSINERGIC-R AND ENOS

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Obesity is growing globally in developing and developed countries. Intake of high calorie diet leads to vital organ dysfunctions due to alterations in various biochemical and histological parameters. Our study signifies that intake of high fat diet (HFD), results in escalation of morphological parameters, lipid parameters and glucose level. Increased HFD intake culminates cardiac dysfunctions, hepatic impairment, renal in-

juries, elevated oxidative stress and alterations in histopathology. Treatment with *fluvoxamine* attenuates the vital organ dysfunctions and same was reversed by *BADGE*, *caffeine* and *L-NAME*. Hence, it has been proved the mechanistic role of fluvoxamine in high fat diet induced vital organ dysfunctions in rats through PPAR- γ , adenosinergic receptors and eNOS.

DIETARY BIOACTIVE COMPOUNDS AND THEIR ABILITY TO INDUCE WHITE ADIPOSE TISSUE

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White adipose tissue (WAT) can differentiate into beige adipose tissue by the browning process. Some polyphenols, including isoflavones, particularly genistein, are suggested to increase the expression of browning markers. There is evidence that consumption of genistein can attenuate body weight gain and improve glucose tolerance and blood lipid levels. We have demonstrated that genistein can stimulate the browning process by at least two mechanisms. An indirect mechanism was involved in the induction of PGC-1 α /FND5 in skeletal muscle leading to an increase in the myokine irisin. In preadipocytes, irisin can increase the expression of *Ucp1* and *Tmem26*,

markers of browning, to increase energy expenditure. Genistein was also able to activate browning by a direct mechanism. Incubation of preadipocytes with genistein increased UCP1 expression as well as some biomarkers of browning in a concentration-dependent manner, possibly via phosphorylation of AMPK. The effect of genistein was accompanied by an increase in the number of mitochondria as well as in the maximum respiration rate of the adipocytes. In conclusion, genistein can increase energy expenditure by stimulating the browning process directly in preadipocytes and indirectly by increasing the circulating levels of irisin.

MULTIPLE FACES OF ADIPOSE INFLAMMATION: MORPHOLOGICAL ANALYSIS OF CLINICAL CASES

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Human adipose tissue is partitioned into two large depots (visceral and subcutaneous) and many small depots associated with various organs. Recent evidence accumulated about the role of adipose tissue in variety of pathological processes ranging from cardiometabolic to neurodegenerative and oncological diseases. However, data in regard to histology of adipose inflammation in cellulitis is surprisingly few. The range of adipose inflammation in cellulitis encompasses a broad spectrum – from severe life-threatening conditions to wide-spread cosmetic defects. Acute cellulitis is a bacterial infection involving the dermis and the hipoderma. Although the term “cellulitis” refers specifically to a skin infection, the chronic variant is also known as “orange peel skin”, closely related to the loss of skin firmness and fatty accumulation in the hipoderma. Cellulitis, both acute and chronic, is a matter of

consideration predominantly on the basis of etiology, clinical course, treatment and mortality. Here we provide histological results from human biopsy and postmortem examinations of eight clinical cases of infectious and non-infectious cellulitis and two cases of inflammation of the epicardial adipose tissue. In the area of acute inflammation adipocytes are surrounded by various types of inflammatory cells, predominantly polymorphonuclears, and undergo necrosis, size change and small blood vessel vasculitis. In case of chronic cellulitis, the adipose tissue is infiltrated by inflammatory cells such as macrophages and lymphocytes and show areas of fibrosis. It is suggested that inflammatory processes, especially in the long lasting chronic cellulitis, probably contribute to modulation in the synthetic and secretory activities of adipose tissue cells or, *vice versa*.

BENEFITS OF HUMAN AND BOVINE COLOSTRUM IN HEALTH AND DISEASE

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Human and mammalian newborns receive colostrum from their mothers during the first 24- 48 hrs after birth. Since colostrum is secreted in more concentrated form during the first 8 hrs post-delivery, the readily available naturally produced nutrients and antibodies are delivered to the suckling newborn in a highly-concentrated and low-volume format. Some mothers may not be able to breastfeed their babies, and their infants may get the necessary bioactive ingredients present in bovine colostrum (BC). There is emerging evidence that BC may be one of the promising nutraceuticals which can prevent or mitigate various diseases in newborns and adults. Immunoglobulins, lactoferrin, and other important nutrients present in colostrum are known to build natural life-long immunity in newborns, which helps to reduce mortality in this population. It has been reported that BC has more than 100- to 1000- folds higher nutritional value as opposed to human colostrum. BC is rich in immunoglobulins, lactoferrin, anti-oxidant, anti-inflammation, anti-microbial, immune boosting, and growth

promoting factors, which enhance tissue growth and maturation of the digestive tract and immune function in human and animal neonates. As opposed to milk, BC has lesser amount of lactose, and therefore may be suitable for patients suffering from lactose intolerance. Limited number of clinical studies done in humans and animals with BC supplements has shown promising results for curing diseases like AIDS, cardiovascular and gastrointestinal disorders, infectious diseases, wound healing, and certain cancers. BC seems to be a treasure trove which if tapped could confer many health benefits and cost-effective cures in humans. However, well-designed, randomized, double-blind, placebo-controlled studies with BC products are needed to widen their therapeutic role. The objectives of this communication are to create awareness about the nutraceutical properties of BC, and to discuss the various prophylactic and therapeutic applications of BC and its bioactive ingredients in humans.

HYPOTHALAMIC INTEGRATION OF ENERGY METABOLISM

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The brain is in charge of controlling our behavior and physiology; nothing inside our body takes place without that the brain is informed. Sensory metabolic information to the brain is transmitted via the blood stream and via sensory nerve endings in our organs, such as the stomach, liver, fat tissue or muscles. This information is conveyed to hypothalamic centers where decisions are made resulting in behavioral action or changes in physiology and associated hormonal or metabolic balances. In principle this leads to a perfect homeostasis whereby food intake and energy expenditure keep each other in balance. Thus the question arises why in so many conditions this balance is not achieved. To answer this question it is important to realize that the received feedback can be overruled by other areas of the brain that may ignore the signals of the hypothalamus. Important for a balance in metabolism is: 1. food intake should not exceed the daily metabolic need, and 2. Food should be taken at the right time of the day. For both conditions several hypothalamic mechanisms have been

developed that are in general the same in most mammalian species. One system, the arcuate nucleus, is especially involved in the sensing of short term and long term metabolic balance, taking into account the amount of body fat and the levels of circulating glucose. The other system, the suprachiasmatic nucleus or circadian system, takes into account, when to eat, so that digestion takes place at an optimal time. Interestingly there is a close interaction between the circadian system and the arcuate nucleus whereby the exchange of information leads to an adequate setting of metabolic conditions. This interaction leads to an organized output of the hypothalamus adapting behavior and physiology according to the time and the metabolic status of the individual. When the individual decides to ignore the signals of the arcuate and circadian system resulting in aberrant food intake both in quantity and time, this will also result in undesired physiological changes. Violating frequently these hypothalamic signals will result in obesity and metabolic syndrome.

PROLACTIN PROMOTES ADIPOCYTE FUNCTION, ADIPOSE TISSUE FITNESS AND METABOLIC HOMEOSTASIS: IMPLICATIONS FOR OBESITY

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The hormone prolactin (PRL) promotes adaptive changes under metabolic challenge. Prolactin (PRL) circulating levels are reduced in patients and rodents with insulin resistance, whereas PRL treatment promotes systemic insulin sensitivity and adipose tissue healthy expansion in high fat diet (HFD)-fed rats. In agreement, PRL receptor (PRLR) null mice subjected to HFD show aggravated insulin resistance and adiposity. The effects of PRL promoting metabolic homeostasis and adipose tissue fitness involve direct actions on preadipocytes and adipocytes. Reduced PRLR expression in primary preadipocytes by shRNA-lentiviral vectors diminishes the expression of the key adipogenic transcription factors: peroxisome proliferator-activated receptor gamma (PPAR γ) and CCAAT/enhancer-binding protein alpha (C/EBP α), in turn, preventing differentiation into mature adipocytes. Likewise, down-regulation of PRLR expression in mature adipocytes results in decreased expression of genes relevant for adipocyte function

such as PPAR γ , Glucose Transporter 4 (GLUT4), adiponectin, and leptin. Furthermore, PRL is able to prevent tumor necrosis factor α -induced insulin resistance in cultured adipocytes, by increasing AKT phosphorylation, particularly in cells from the visceral adipose depot. Finally, lower PRL serum levels correlate with insulin resistance and visceral fat adipocyte hypertrophy in humans. Altogether, our findings demonstrate that PRL promotes adipose tissue fitness via stimulating adipocyte differentiation, function, and insulin sensitivity. Because, high PRL circulating levels, within the physiological range, are required to maintain metabolic homeostasis, PRL enhancing drugs have therapeutic potential in obesity-related metabolic diseases.

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VISUALIZING THE METABOLIC RESPONSES OF STIMULATED NEURONS USING GENETICALLY-ENCODED BIOSENSORS AND FLUORESCENCE LIFETIME MICROSCOPY

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Energy utilization by the brain is both high and highly dynamic. During brain excitation, the local increases in both blood flow and glucose consumption substantially exceed the increase in oxygen consumption in the activated area. This mismatch suggests that glycolysis transiently surpasses the capacity of fuel oxidation by the mitochondria, resulting in lactate production. However, the cellular site of this aerobic glycolysis is still controversial. A popular hypothesis proposes that glycolysis is elevated in astrocytes, which then transfer lactate to neurons for its oxidation. To determine if neurons utilize lactate or perform aerobic glycolysis during stimulation, we expressed genetically-encoded fluorescence lifetime biosensors in dentate granule neurons (DGNs) from acute hippocampal slices. These sensors allow the quantitative assessment of cellular metabolism with high spatial and temporal resolution. We measured the cytosolic NADH/NAD⁺ ratio (NADH_{CYT}) in neurons using the sensor Peredox, along with the Ca²⁺ sensor RCaMP1h as readout of neuronal activity. We find that the transient increase in NADH_{CYT} correlates with the level of activity in neurons, for both synaptic and antidromic stimulation. Blockade of monocarboxylate transporters

(MCTs) does not abolish this increase, as predicted from the idea of lactate transfer from astrocytes, but rather enhances the increase of NADH_{CYT} in stimulated DGNs. This result indicates that the neuronal metabolic response does not depend on lactate uptake; instead, neurons are likely to perform glycolysis and to be exporters of lactate during activation. Using the glucose sensor iGlucoSnFR-TS (formerly called SweetieTS), we observed small transient drops in [glucose]_i that had a very similar time course to the NADH_{CYT} transients, and their behavior was consistent with increased neuronal consumption of glucose. Changes in [glucose]_i are also influenced by NADH-to-NAD⁺ recycling in neurons: MCT inhibition decreases the stimulation-induced dips reported by the glucose sensor. Taken together, our results suggest that neurons rely on glucose rather than astrocytic lactate during stimulation.

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EFFECT OF ANG II ON THE INSULIN SIGNALING PATHWAY IN ADIPOSE CELLS

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In adipose tissue, insulin exerts a myriad of effects associated with the regulation of lipid and glucose metabolism, being responsible for maintaining energy balance. The decrease in the insulin response in adipose cells leads to an imbalance that is associated with various metabolic diseases. In this context, studies performed in patients with metabolic syndrome showed that the levels of Angiotensin II (Ang II), an octapeptide generated by the renin-angiotensin system (RAS), are increased in adipose tissue; suggesting that, this hormone is involved in the pathogenesis of obesity and insulin resistance. However, the mechanism associated with Ang II actions on insulin signaling in fat cells is still unclear. Thus, our work is focused on demonstrating the regulatory mechanism that Ang II exerts in fat cells on insulin signaling in 3T3-L1 adipocytes and epididymal adipocytes isolated from mice. We found that in 3T3-L1 adipocytes, Ang II impairs insulin signaling at the level of the IR and Akt activation as well the insulin-induced glucose uptake. These inhibitory actions were associated with

increased phosphorylation of the insulin receptor at serine residues. Interestingly, angiotensin II-induced serine phosphorylation of IRS was not detected; suggesting that angiotensin II-induced desensitization begins at the regulation of insulin receptor itself. PKC inhibition by BIM (a PKC inhibitor) restored the inhibitory effect of angiotensin II on insulin-stimulated tyrosine phosphorylation of IR, glucose uptake, and Akt inactivation. These results suggest that angiotensin II may lead to insulin resistance through PKC activation in 3T3-L1 adipocytes. Finally, in adipose cells isolated from mouse epididymal tissue, we confirm the decrease in the insulin signaling with the consequent reduction of the phosphorylation in proteins located downstream of the signaling cascade as Akt.

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CIRCADIAN DISRUPTION AS A RISK FACTOR FOR HIGH ADIPOSITY

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Shift-work, frequent transmeridional traveling, shifted sleep time and light at night are conditions that lead to circadian disruption and loss of behavioral and physiological homeostasis. Individual exposed constantly to such disruption are at risk to develop overweight and metabolic disturbance. In order to better understand the mechanisms that lead to the loss of homeostatic balance we have developed experimental models with rodents. A main effect observed with all models is an increased adiposity and dyslipidemia. We have observed that animals exposed to protocols of circadian disruption, shift their feeding schedules to the hours when they are forced to be awake, even when this timing is in conflict with the light-dark cycle. Therefore, we have exposed animals to restricted feeding schedules of 12 h fasting – 12h food. When food was scheduled to the normal activity phase, which is night for ro-

dents, the feeding schedule restored circadian rhythmicity and prevented overweight and dyslipidemia. However, when food was scheduled out of phase from the normal light-dark cycle, it triggered deleterious effects on metabolism and body weight.

We will present experimental evidence of deleterious effects of disrupted circadian rhythms on metabolism and bodyweight and will point out the relevance of the timing of food intake. We will further discuss the benefits and limitations of feeding schedules to ameliorate the metabolic burden in shift workers and other individuals affected by circadian disruption.

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AAV-MEDIATED INHIBITION OF GLRX1 IN MOUSE SKELETAL MUSCLE: A THERAPEUTIC APPROACH TO IMPROVE ISCHEMIC LIMB

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Diabetes is a critical risk factor for the development of peripheral artery disease. Patients with type-2 diabetes have impaired blood flow recovery in response to ischemia compared with non-diabetic subjects. We reported that glutaredoxin-1 (Glxr) deletion promotes vascularization via HIF-1 α stabilization after hindlimb ischemia, indicating that Glxr acts as an anti-angiogenic enzyme, which also regulates redox signaling. Adeno-associated viruses (AAVs) have been particularly enticing for human gene therapy due to their transduction efficiency, safety, and stable gene expression. The primary goal of this project was to inhibit Glxr protein levels specifically in the skeletal muscle using AAVs. HEK293T cells were co-transfected using a helper-free AAV system, and a bicistronic expression system encoding a short hairpin RNA (shRNA) against Glxr or a control shRNA sequence, and mVenus, a fluorescent protein used as reporter. AAVs were purified from medium and cell lysates by polyethylene glycol precipitation,

aqueous two-phase partitioning, and an iodixanol gradient. Titters and purity of AAVs were determined by qPCR and silver staining, respectively. C2C12 cells and C57Bl/6 mice were used to test the viral preparations. The optimized protocol yielded viral preparations with titers of 10¹⁰-10¹¹ viral genome copies per μ L, and more than 90% of purity, suitable for *in vivo* studies. Transduced C2C12 cells exhibited a ~75% decrease in Glxr expression and protein levels, four days after infection. Intramuscular injection of AAV6 in the mouse gastrocnemius efficiently transduced the reporter mVenus, which was not detected in heart, liver, or the gastrocnemius from the non-injected limb. Three weeks post injection, Glxr protein levels remained unchanged, but after six weeks, Glxr mRNA and protein levels decreased by 80% and 50%, respectively. Successful inhibition of Glxr in the medial thigh constitutes the first step in our strategy for improving blood flow recovery after hindlimb ischemia in diabetic mice.

HIGH-INTENSITY INTERVAL TRAINING REDUCTION OF CROWN-LIKE STRUCTURES IN ADIPOSE TISSUE

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Obese adipose tissue is infiltrated by macrophages where they surround dead adipocytes resulting in a characteristic morphological crown-like structure (CLS). In the adipose tissue macrophages release cytokines and constitute part of the mechanisms by which obesity results in an increased cardiovascular and type 2 diabetes risk. Exercise, recommended for the treatment of obesity and reduction of the metabolic risk, reduces the presence of CLS in adipose tissue. Recently high-intensity interval training (HIIT) has emerged as a more efficient alternative to traditional moderate-intensity continuous training (MICT). Thus, we aimed to compare the amount of CLS reduction in the adipose tissue of rats with metabolic syndrome that underwent these exercise protocols. Young adult male Wistar rats were housed in standard conditions and divided into four groups. First group was control and had food and water *ad libitum*. The three remaining groups had water replaced by a 20% sucrose solution. The four groups re-

ceived this treatment for 12 weeks after which the sucrose fed groups underwent MICT, HIIT or no exercise for 8 weeks. At the endpoint metabolic syndrome measurements were taken and adipose tissue was collected for histological examination. Hematoxylin and eosin, and immunohistochemistry for F4/80 macrophage marker were performed to observe CLS. Obtained images were analyzed with FIJI software for adipocyte size, CLS count and immunohistochemical staining. Sucrose fed group adipose tissue exhibited large adipocytes and abundant F4/80 staining was visible while control group had scarce staining and smaller mean adipocyte size. Both exercise groups had a comparable decrease of the macrophage staining, and adipocyte size that was correlated with assessment of metabolic syndrome. HIIT appears to be as effective as MICT for the reduction of adipocyte size and macrophage infiltration of the adipose tissue and this reduction is accompanied with an improvement of metabolic syndrome indicators.

PHARMACOLOGICAL MODULATION OF OSTEOCALCIN LEVELS: OPPOSITE METABOLIC EFFECTS OF *WARFARIN* AND *ALENDRONATE*

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Recent experimental evidence implicates the bone-derived vitamin K-dependent protein osteocalcin (OC) in regulation of energy metabolism. Undercarboxylated osteocalcin (ucOC), released in blood during bone resorption, is postulated to stimulate insulin secretion and to increase insulin sensitivity. These findings raise variety of questions, including pharmacological in nature. The present work aimed at studying whether pharmacological modulation of ucOC serum levels could produce metabolic changes. Thus, we examined the effects of two drugs of wide clinical use: (i) the vitamin K antagonist *warfarin* and (ii) the anti-resorptive anti-osteoporotic bisphosphonate drug *alendronate*. Four groups of male rats were treated for 4-6 weeks with: (i) high dose of *warfarin* by oral gavage plus a protective dose of *vitamin K1* to prevent bleeding; (ii) *alendronate* by s.c. injection; and (iii-iv) vehicles for each treatment. At the end of the experiments insulin-tolerance test was performed by measuring blood sugar at 0, 30, 60

and 90 minutes after an i.p. insulin injection. Adipose index was determined as the retroperitoneal adipose mass to body weight ratio. Serum ucOC was measured by an ELISA kit. Chronic treatment with *warfarin* caused a pronounced elevation of ucOC. This was associated with borderline decrease in blood sugar and improvement of insulin sensitivity. The adipose index decreased significantly. Chronic administration of *alendronate* resulted in significant reduction of ucOC. Blood glucose was elevated and insulin sensitivity was impaired. The increase of adipose index did not reach statistical significance. In effect, *warfarin* and *alendronate* induced opposite changes in serum ucOC levels and these were accompanied by corresponding alterations in markers of energy metabolism. Caution is needed in the clinical interpretation of these findings. Studies in humans are limited and the available data are inconsistent.

THE EFFECT OF SELECTED INCRETIN DRUGS ON ADMA METABOLISM IN CARDIOVASCULAR SYSTEM OF FRUCTOSE-FED RATS

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High level of circulating asymmetric dimethylarginine (ADMA), an endogenous inhibitor of nitric oxide (NO) synthesis, is a risk factor for endothelial dysfunction and cardiovascular disease (CVD) development. ADMA is synthesized by protein-N-methyltransferase 1 (PRMT1) and catalysed by dimethylarginine dimethylaminohydrolases (DDAH1,2). The major route of ADMA elimination from circulation is its renal uptake and degradation. The tight enzymatic control of ADMA metabolism may be dysregulated in insulin resistance and diabetes. Therefore, the aim of this study was to evaluate whether dipeptidylpeptidase-4 inhibitor (sitagliptin) and glucagonlike peptide 1 analogue (exenatide) may affect ADMA metabolism in kidney and heart of rats with fructose induced metabolic syndrome.

Normal (CON) and fructose-fed (FRU) rats were treated for 4 weeks with sitagliptin (S) (5.0 and 10 mg/kg p.o) or with exenatide (E) (5 and 10 µg/kg, s.c.). The activity of tissue DDAH was measured spectrophotometrically. The concentration of plasma NO, ADMA and tissue DDAH1, DDAH2, PRMT1 protein were measured by enzyme immunoassay

technique. Myocardial *DDAH1* and *DDAH2* expressions were assessed by RT-PCR analyses.

The significant increase of ADMA (+27,0%) and decrease of NO (-57,4%) concentrations were found in plasma of fructose-fed (FRU) rats vs control (CON). Exenatide administration reduced plasma ADMA level by 39,7% (FRU+E5) and 38,5% (FRU+E10) vs FRU, respectively. Both, sitagliptin and exenatide treatment caused significant increase in NO concentration: FRU+S5 (+111,7%); FRU+S10 (+100,9%); FRU+E5 (+97,1%) and FRU+E10 (+100,9%) vs FRU. In the kidney, there was significant increase in DDAH activity after both, sitagliptin (+47,8%; FRU+S10) and exenatide (72,5+%; FRU+E5 and +45,1%; FRU+E10) treatment vs FRU. By contrast, the sitagliptin treatment resulted in myocardial DDAH activity reduction (-66%; FRU+S5 vs FRU), whereas exenatide increased the PRMT1 mass (+60%) in FRU+E10 vs FRU. In fructose-fed rats, both sitagliptin and exenatide improve ADMA hydrolytic elimination in the kidney but have no beneficial effect on enzymatic control of its metabolism in the heart.

IMPACT OF MATERNAL OVER-NUTRITION DURING PREGNANCY ON THE CIRCADIAN REGULATION OF CORE BODY TEMPERATURE IN LACTATING RABBITS

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Metabolic parameters ranging from circulating nutrient levels and substrate utilization to energy expenditure and thermogenesis are temporally modulated by the circadian timing system. During critical embryonic developmental periods, maternal over-nutrition, could alter key elements in different tissues associated with the generation of circadian rhythmicity, compromising normal circadian rhythmicity at birth. To address this issue, we used a rabbit model to determine whether maternal over-nutrition leads to alterations in the development of circadian rhythmicity at physiological and behavioral levels in the offspring. For this, female rabbits were fed a standard diet (SD) or high-fat and carbohydrate diet (HFCD) before mating and during gestation. At birth, newborn rabbits were maintained under a light: dark cycle and nursed by foster mothers (that were fed SD). From lactation to weaning, their core body temperature and gross locomotor activity were continuously recorded through telemetry, and daily measurement of body weight and the amount of milk ingested by the pups was carried out. At the end of lactation, a group of animals was killed, and blood and tissue samples, including brown adipose tissue (BAT) and white adipose tissue (WAT) samples, were

obtained for determining the levels of uncoupling protein-1 (UCP1) and cell death-inducing DNA fragmentation factor-like effector A (CIDEA).

HFCD pups exhibited conspicuous differences in the development of the daily rhythm of temperature and locomotor activity compared to the SD pups, including a significant increase in the daily mean core temperature, changes in the time when temperature or activity remains above the average, shifts in the acrophase, decrease in the duration and intensity of the anticipatory component, and changes in the most energetic components of the rhythms. HFCD pups exhibited a significant increase in BAT thermogenesis markers and a decrease of these markers in WAT, indicating less heat generation by brown adipocytes and alterations in the browning process. These results clearly indicate that maternal over-nutrition alters offspring homeostatic and chronostatic regulation at the physiological and behavioral levels. Further studies are needed to accurately determine whether alterations in environmental factor during gestation are associated with the changes in the organization of the circadian system of the progeny.

INFLAMMATORY MARKERS IN THE SERUM OF ADULT SUBJECTS WITH 22Q11.2 DELETION SYNDROME

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DiGeorge syndrome (1,2), also known as 22q11.2 deletion syndrome, is a syndrome caused by the deletion of a small segment of chromosome 22. While the symptoms can vary, they often include congenital cardiovascular problems, specific facial features, frequent infections, developmental delay, learning problems and cleft palate. Associated conditions include kidney problems, significant feeding and metabolic problems, hearing loss and autoimmune disorders. DiGeorge syndrome occurs in about 1 in 4,000 people. Since nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) are known to play subtle roles in the regulation of oxidative, cardiometabolic and immune physiological related events (3–5), in this study we evaluated NGF and BDNF serum levels of and some markers of oxidative stress in subjects with DiGeorge syndrome. The sample population consisted of 14 men and 4 women diagnosed by both a geneticist and a molecular analysis. Twenty healthy men and 11 healthy women were included in the study as controls. Venous blood samples were collected and NGF and BDNF levels were measured by ELISA assay. The mean NGF serum levels of DiGeorge syndrome patients were significantly lower compared to controls in absence of gender differences. However, BDNF serum levels were not significantly altered compared to controls. Oxidative stress was analyzed as free oxygen radicals defense (FORD) and free oxygen radicals test (FORT) in association with a panel of 8 cytokines whose expression levels are strongly influenced by NGF/BDNF. Data show that in DiGeorge syndrome serum Interleukin (IL)-1 β , IL-2, IL-6 and IL-12 were significantly reduced. Quite inter-

estingly serum FORT in DiGeorge syndrome was potentiated but only in those subjects under treatment for mood regulators. Our study suggests a potential role of the NGF pathway as marker for appropriate treatment of immune, metabolic and central nervous systems trophic disconnections in DiGeorge syndrome.

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WAIST-TO-HEIGHT RATIO, RELATIVE FAT MASS AND CARDIOMETABOLIC FACTORS IN PATIENTS OF A YUCATAN TERTIARY CLINIC

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It is widely accepted that body composition is an essential part of the check up for preventing complications associated to the excess of adipose tissue. According to the Mexican Health Survey (ENSANUT-MC-2016), the country south-eastern shows one of the highest rates of overweight and associated morbidities (i.e. diabetes). In this study we evaluated the Waist/Height ratio (W/Hr) as a better indicator, applicable to any population, than body mass index (BMI) for cardiometabolic risk. Also, we used a new Relative Fat Mass (RFM) linear equation, as a tool to estimate whole-body fat percentage that has high correlation with DXA in adult population of Mexican-Americans. The present study is cross-sectional, with 100 participants (76 women and 24 men) from a tertiary clinic, who were surveyed for lifestyle, body composition and serum biochemical determinations (glucose, triglycerides, total cholesterol (TC), cholesterol-HDL, cholesterol-LDL, urea, creatinine, insulin) and atherogenic index. The mean age was 48.03 ± 10.76 years old, and 54% fulfilled the criteria (ac-

cording to NCEP-ATPIII) for metabolic syndrome (MetS). We performed correlation analyses of W/Hr and BMI with the main indicators for MetS and the results showed positive significant correlation with RFM ($p < 0.001$, for both indexes), diastolic pressure (DBP) ($p = 0.013$, $p = 0.021$, respectively), insulin ($p = 0.002$, $p < 0.001$, respectively), and only W/Hr showed significant positive correlation with glycaemia ($p = 0.012$). For mean comparisons, we split the sample in two groups of W/Hr (< 0.6 and > 0.6 , $n = 48$ and $n = 52$, respectively), and two groups of BMI (< 25 and > 25 , $n = 16$ and $n = 84$, respectively). The results for W/Hr > 0.6 were higher glycaemia ($p = 0.006$), insulin ($p = 0.006$), DBP ($p = 0.009$), and RFM ($p < 0.001$). For BMI > 25 , higher insulin ($p = 0.002$), TC ($p = 0.009$), LDL ($p = 0.012$), triglycerides ($p = 0.024$) and RFM ($p < 0.001$). In conclusion, W/Hr and BMI had significant association with markers of MetS, however only W/Hr was consistently associated with glycaemia, and both with, at least, one dyslipidemia indicator.

AQP7 REGULATION BY GLUCOCORTICOIDS IN WHITE AND BROWN ADIPOCYTES

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The regulation by glucocorticoid hormones (GCs) is essential in biological processes such as development, immunity and energy metabolism. Aquaporin 7 (AQP7) is the primary glycerol transporter in white (WAT) and brown (BAT) adipose tissues. With the aim to compare the action of cortisone over the expression of AQP7, and to test if there were differences between white adipocytes (WA) and brown adipocytes (BA), two different primary cultures from CD-1 mice were performed. Brown adipose tissue from 1-day old mice was dissected and digested for precursors' extraction and 21-day old mice subcutaneous WAT was dissected to obtain white precursors. All cell culture assays were differentiated into white or brown adipocytes and, once differentiated, cortisone response was characterized (0.1, 1 and 10 M), at 5 different times (0, 5, 10, 15, 20 minutes and 48 hours). In addition, the human SGBS cell line was employed; these precursor cells were differentiated into white adipocytes in order to characterize potential differences

between mice and human cells. Gene expression was measured by qPCR and the relative abundance of specific mRNAs was calculated using the $2^{-\Delta\Delta CT}$ method. There were immediate and quantitatively important actions of cortisone over the expression of AQP7 in murine and human adipocytes. Short-term response (minutes) of cortisone treatment resulted in AQP7 mRNA overexpression in white and brown differentiated adipocytes (between 1.5 and 6 fold). Conversely, long-term response (hours or days) resulted in decreased mRNA expression. The effects observed on AQP7 mRNA expression upon cortisone treatment in brown and white differentiated adipocytes were concordant with those observed for glycerol kinase mRNA and 11 β -hydroxysteroid dehydrogenase type 1 mRNA. The regulatory pathways in the distinct adipose depots-derived cells should be better characterized in order to clarify the role of GCs on aquaporins and its relevance in the development of metabolic diseases.

DNA METHYLATION DETERMINE ADIPOGENIC POTENTIAL OF DENTAL TISSUE-DERIVED STEM CELLS

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Obesity is a rising public health problem related to develop type 2 diabetes mellitus, cardiovascular diseases and cancer. With adipose precursors found outside of adipose depots (muscle, bone marrow, pericardium and others) it is clear that its expansion due to obesity might have a negative impact on human health. Therefore, the characterization of adipogenic commitment among different adipocytes depots requires further research.

At like that human dental tissue-derived mesenchymal stem cells (hDT-MSCs), a subset of adipocytes originates from neural crest cells; therefore we reasoned that using these mesenchymal stem cells (MSCs) might be an entry point to understand the molecular mechanisms governing adipogenesis. MSC adipogenesis is quite complex and their full transcriptional control remains unclear. DNA methylation is a crucial mechanism in the regulation of gene expression and is necessary for controlling stem cell differentiation. But its contribution in the establishment of final cell fate decision is still

unclear. Therefore, the main goal of this study was to identify whether DNA methylation patterns between two cell lines of hDT-MSCs influences their cell plasticity. In the present study, we compared the morphological characteristics and the adipogenic differentiation of hDT-MSCs such as periodontal ligament stem cells (PLSCs) and dental pulp stem cells (DPSCs). We found that these cells displayed important differences in their adipogenic differentiation capacity. By using gene expression analysis, we found that *PPARγ*, a master transcriptional adipogenic factor, and *DNMT1*, a major DNA methyltransferase, was down- and upregulated in DPSCs. Moreover, in order to know the DNA methylation status of several adipogenic genes among different cell lines, we used DNA methylation database and bioinformatic tools to correlate DNA methylation and adipogenesis potential of hDT-MSCs, for subsequent DNA bisulfite sequencing analysis. Together, these results will be leading to determine the role of DNA methylation in the adipogenic potential of hDT-MSCs.

PERIODONTAL STEM CELLS AS STUDY MODEL FOR ADIPOGENESIS

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Adipogenesis consists of two stages; the first is designated as “determination” which is characterized by the commitment of a pluripotent stem cell (SC) to the adipogenic lineage, while the second stage is called “terminal differentiation”, where the pre-adipocytes acquire the phenotype of a mature adipocyte. Currently, the *in vitro* models used to study adipogenesis are essential to understand the molecular mechanisms involved in this process and even though terminal differentiation has been studied extensively in the 3T3-L1/F442A lines, there are few reports focused on studying the determination stage. The objective of this work is to establish an *in vitro* model that allows the analysis of adipogenic differentiation through the culture of stem cells derived from the periodontal ligament (PLSC). For this, the periodontal ligament of a third molar from a male patient with 18 years old was obtained previous informed consent. Afterwards, the cells were isolated by the

explant method. Subsequently, the characterization of the PLSD was performed. For adipogenic induction, the cells were seeded in multi-well plates and incubated under controlled conditions for 21 days. The identification of lipid droplets in the cells was done by staining with red oil and microscopic observation. The characterization of the PLSCs showed morphology like fibroblasts and clonogenic populations, as well as the expression of pluripotency markers. The kinetic parameters of the *in vitro* culture suggest that their growth rate is high and that they maintain their viability during the culture period. On the other hand, a positive response to adipogenic differentiation was detected since the microscopic examination showed the presence of lipid vacuoles. In conclusion, the CTLP have a great cellular plasticity towards the adipogenic lineage which would allow to realize studies about the molecular mechanisms involved during the process of adipogenesis.

MECHANISM OF THE ANTI-DIABETIC ACTIVITY OF *TERMINALIA ARGENTEA* (COMBRETACEA) IN TYPE 2 DIABETIC MICE

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The present study aimed at investigating the potential anti-diabetic effect of *Terminalia argentea*. The crude ethanolic extract (CEE) from the leaves of *T. argentea*, its ethyl acetate (EAF) and hydro-methanolic (HMF) fractions were screened for the inhibition of α -glucosidase, α -amylase, and lipase activities, as well as on oral starch tolerance (OSTT) and hypoglycemic tests. T2DM was induced in male Swiss mice by intraperitoneal injection of nicotinamide (130 mg/kg) plus streptozotocin (150 mg/kg) two weeks after daily addition of fructose (10%) in drinking water. Four weeks later, mice with blood glucose level superior to 200 mg/dL started treatment with CEE and EAF (100 mg/kg/per day) by gavage for 28 days. After the treatment, the oral glucose tolerance test (OGTT) was performed. Serum parameters such as HbA1c, glucose, total cholesterol (TC), triglyceride (TG), and uric acid were measured. Glucose and creatinine were also measured in the urine. Serum alanine transaminase (ALT) and as-

partate transaminase (AST) were also measured to assess liver function. CEE, EAF and HMF concentration-dependently inhibited the activity of α -glucosidase (pIC_{50} = 5.46 ± 0.03 , 5.76 ± 0.05 , and 5.73 ± 0.03 , respectively), α -amylase (pIC_{50} = 4.15 ± 0.18 , 4.77 ± 0.20 , and 4.06 ± 0.16 , respectively), and lipase (pIC_{50} = 3.97 ± 0.12 , 3.87 ± 0.04 , 3.67 ± 0.14 , respectively). Blood glucose was significantly reduced by oral administration of 100 mg/kg CEE, EAF, and HMF on OSTT, while only CEE significantly reduced glycemia after 1 hour on the hypoglycemic test. In T2DM mice, CEE and EAF improved glucose tolerance, significantly reduced blood glucose, HbA1c, uric acid, and creatinine, ALT, AST, TC, and TG levels. However, they did not change urine glucose and creatinine levels. The present results demonstrate that *Terminalia argentea* has an anti-diabetic activity with a significant effect on metabolic and liver parameters. Inhibition of α -glucosidase contributes to the mechanism of action of *T. argentea*.

CHARACTERIZATION OF ADIPOSE TISSUE BY BIOPHOTONICS TECHNIQUES

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Recently, Biophotonics techniques have emerged as an alternative tool in the analysis of biological tissues. In this work we propose the use of Raman spectroscopy (RS) and infrared thermography (IRT) to characterize spectral differences in adipose tissue of control, diabetic and obese rats. The main advantage of using RS combined with IRT in adipose tissue lies in the fact that these two techniques provide complementary information. RS provides information on changes in the molecular structure of the adipose tissue and IRT detect changes in the temperature related to energy metabolism of adipose tissue. To our knowledge, there is not published work that refers to the characterization of adipose tissue combining RS and IRT on rat model. In our work, RS and IRT of three different groups of rats (control, obese, type I diabetes) was evaluated. Before sacrifice, subjects were examined using an infrared camera to know the exact temperature of adipose tissue at

the same anatomical location. After animals were euthanized, adipose tissue samples were extracted, and the Raman spectra were obtained. The RS data were analyzed using principal component analysis (PCA) and we find the first two principal components provide information to discriminate between the three groups without the need of a priori information, only based on spectral features of each group. IRT results show an increase in temperature in obese group (temperature average of 35.9°C) and a decrease in type 1 diabetes group (temperature average of 32.5°C) relative to controls. In conclusion, the results show that RS combined with PCA is relatively simple, fast and can be used in the characterization of adipose tissue. Thermal imaging showed a specific thermal behavior of the adipose tissue in obese rats and may also be used as a non-invasive way of distinguishing among different adipose tissue specimens.

FTO GENE VARIATION: SNP *RS1421085*, *RS8057044*, *RS9939609* IN MEXICAN MAYAN CHILDREN WITH OBESITY OR OVERWEIGHT

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Genetic variants within the *FTO* gene have been identified as risk factors with strong effects on variation of the human body mass and body composition. We evaluated the association of the *FTO* SNPs *rs1421085*, *rs9939609*, *rs8057044*, with the risk for obesity or overweight in Mexican school-aged children with Mayan ethnicity, where childhood obesity is highly prevalent. We performed a case-control association study including 318 children with obesity or overweight; and 303 children with normal weight. *FTO* SNPs were genotyped using real-time PCR. *FTO* genetic variants' effect on a child with overweight/obesity was assessed using a univariate and multivariate non-conditional logistic regression models adjusted for gender. Heterozygous genotype CT and allele C for *FTO rs1421085* were associated with the highest genetic risk of having childhood obesity (OR: 1.96, IC 1.26-3.05, $p=0.003$). Ad-

justing by gender, we obtained significant genetic associations' specific to females or males. Heterozygous genotype AT (OR: 1.94, IC 1.12- 3.63, $p=0.023$) and the risk allele A for *rs9939609* (OR: 1.58, IC 1.02-2.46, $p=0.042$), as well as *rs1421085* heterozygous genotype CT (OR: 2.56, IC 1.36-4.79, $p=0.003$) and the risk allele C (OR: 1.98, IC 1.17-3.38.79, $p=0.013$); were significantly associated with the genetic risk for obesity, only in females; whereas *rs8057044*, heterozygous genotype AG (OR: 2.92, IC 1.04-8.20, $p=0.035$) and the risk allele A (OR: 2.28, IC 1.14-4.58, $p=0.021$), were significantly associated with the genetic risk for overweight only in male children. The genetic effect of the *FTO* variants *rs1421085*, *rs9939609*, *rs8057044* is specific about the gender on the genetic basis of obesity and overweight in Mayan school-aged children.

ROLE OF CALPAINS ON GLUT4 TRAFFICKING IN ADIPOCYTES

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Calpains (CAPNs) are a family of calcium-dependent intracellular proteases, and together with their endogenous inhibitor, calpastatin, integrates the calpain system. The calpain system is involved in several cellular processes, such as vesicular trafficking, apoptosis, cell migration and glucose homeostasis. Because CAPN1, CAPN2 and CAPN10 have been implicated in the glucose metabolism, in this work, we evaluated the role of these proteases in GLUT4 trafficking in adipocytes. First, we measured the presence of CAPN1, CAPN2 and CAPN10 in retroperitoneal white adipose tissue, gastrocnemius muscle, liver, heart and pancreas of fed adult mice, showing that the autolysis of CAPN1 and the expression of the isoforms of CAPN10 were higher in white adipose tissue, compared with the other tissues. In the 3T3-L1 cell line, we found that CAPN1, CAPN2 and CAPN10 were differentially expressed during adipocyte differentiation. Calpain activity increased after insulin stimulation in 3T3-L1 adipocytes using a fluoro-

genic calpain substrate peptide (tBoc- Leu-Met-CMAC). The inhibition of calpain activity with the calpain inhibitors AK275 or E64d reduced insulin-stimulated GLUT4 trafficking in 3T3-L1 adipocytes. Moreover, calpain inhibition correlated with an increase of autolytic fragment of CAPN1 and increase of CAPN10 abundance, without changes in CAPN2. We found that CAPN10, but not CAPN1 or CAPN2 colocalize with GLUT4 storage vesicles (GSVs) markers in 3T3-L1 adipocytes. We confirmed the participation of CAPN10 in 3T3-L1 adipocytes by generation of CAPN10 knockdown using a siRNA. CAPN10 knockdown did not induce changes on CAPN1 or CAPN2 expression. We observed that CAPN10 knockdown alters GLUT4 trafficking, suggesting that CAPN10, but not CAPN1 and CAPN2, is related to GLUT4 trafficking. Acknowledgements to CONACYT 254305 and PAPIIT-UNAM IN201914.

CALPAIN-10 PROTEASE REGULATES GLUT4 TRAFFICKING BY PROTEOLYTIC PROCESSING OF TUG IN ADIPOCYTES

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Calpain-10 (CAPN10) is a protease implicated in the insulin-induced trafficking of GLUT4. GLUT4 is retained in the Golgi matrix via the Tether containing a UBX domain for GLUT4 (TUG) protein. Insulin stimulation induces the proteolytic processing of TUG, which leads to the translocation of GLUT4 to the cell membrane. In this study, we assessed whether TUG is a CAPN10 substrate in 3T3-L1 adipocytes. When the TUG proteolysis was analyzed in organs related to glucose homeostasis, we found different fragments of TUG in all tissues tested. In a cell-free system, we showed that TUG protein is cleavage by calpain proteases. As second approach, we evaluated the TUG proteolysis in the modulation of the calpain activity under conditions of stimulation with insulin, a Ca²⁺ ionophore or calpain inhibitors (ALLM, AK275 and E-

64d). We found that insulin-induced TUG proteolysis correlated with the activation of calpains. In addition, we observed that TUG proteolysis was modulated by both Ca²⁺ ionophore and calpain inhibitors. Notably, calpain inhibitors prevented TUG cleavage, resulting in a decrease of insulin-stimulated glucose uptake and in impairment of GLUT4 trafficking. We confirmed that CAPN10 was implicated in TUG proteolysis by transient or stable knockdown of CAPN10, finding that calpain-10 knockdown prevent insulin-induced TUG proteolysis without altering the phosphorylation of Akt. These results provide evidence that TUG protein is cleaved by CAPN10 to regulate GLUT4 trafficking Acknowledgements to CONACYT 254305 and PAPIIT-UNAM IN201914.

ARSENIC INCREASES LIPOGENESIS IN RETROPERITONEAL ADIPOSE TISSUE IN MICE FED HIGH-FAT DIET

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Adipose tissue accumulates fat mainly in the form of triglycerides through *de novo* lipogenesis and/or fatty acid re-esterification. Visceral adipose tissue accumulation has been associated with the development of metabolic diseases such as type 2 diabetes mellitus.

High-calorie diets contribute to excessive triglyceride accumulation in adipocytes. In addition to this factor, some environmental contaminants have been classified as metabolism-disrupting chemicals that promote metabolic diseases. Arsenic, for example, has been proved to be diabetogenic. Nonetheless, little is known about its effects on adipose tissue dysfunctionality in combination with high-fat diet (HFD). Therefore, the purpose of this study is to determine if arsenic favors triglycerides accumulation in different visceral adipose tissue pads predisposing to weight gain and if this effect increases in combination with HFD. C57BL/6 male mice were fed low-fat diet or HFD for 8-weeks. Then, half of each group was exposed to arsenic (100 µg/L) in the drinking water for

additionally 8 weeks, maintaining their same diet. Throughout the study, body weight, food and water intake were measured weekly. At the end, retroperitoneal and epididymal adipose tissues were collected to evaluate tissue weight, adipocytes area, triglyceride content, and mRNA of lipogenic genes. Mice exposed to arsenic had greater body weight gain than their counterpart without arsenic. Mice fed HFD and exposed to arsenic had greatest body weight gain, the largest adipocytes with the highest intracellular triglyceride content in retroperitoneal adipose tissue. Interestingly, arsenic, regardless of the amount of fat in diet, increased the mRNA of the genes involved in *de novo* lipogenesis (SRBP-1c, ACC), in the esterification of fatty acids (DGAT1) and in adipogenesis (PPAR-γ) in retroperitoneal adipose tissue, while decreased them in epididymal adipose tissue. Our data suggest that arsenic favors triglyceride accumulation in retroperitoneal adipose tissue by increasing lipogenesis and in combination with HFD increases the obesity phenotype.

SILYMARIN IMPROVES THE METABOLIC OUTCOME OF OBESE RATS

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Obesity characterizes for the pathological increase in adipose tissue, with hypertrophic adipocytes that secrete pro-inflammatory cytokines and pro-oxidant factors that induce a chronic mild pro-inflammatory state. There are adverse metabolic effects observed during obesity such as hyperglycemia, hyperinsulinemia, glucose intolerance insulin resistance, dyslipidemia, all of these eventually leading to the development of metabolic diseases and diabetes mellitus type 2. The exploration of therapies aimed to counteract the metabolic effects of high-fat diets (HFD) has become a priority in western civilizations. Silymarin is a flavonoid mixture extracted from the *Silybum marianum*, known for its hepato-, neuro-, nephro- and cardio- protective properties, mediated by its anti-inflammatory and anti-oxidant effects. The present study aimed to

evaluate if an intragastric (i.g.) administration of silymarin modulates the metabolic impairments observed in Wistar rats previously fed with HFD for 12 weeks. We observed that 14 days of i.g. administration of silymarin significantly decreased glucose levels in obese rats, even when rats continued consuming the HFD, however, silymarin had no effects in body weight, nor changed the amount of adipose tissue.

Our results suggest that silymarin improves glucose metabolism during obesity in a body weight independent manner.

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SHORT TERM EFFECT OF EARLY POSTNATAL OVERNUTRITION IN TRANSCRIPTOME OF AXIS HYPOTHALAMUS-ADIPOSE TISSUE WISTAR RAT

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Deregulation of the hypothalamus-adipose tissue axis has been reported in metabolic diseases. Recent reports in animal models with hypercaloric diet show changes in neurons that regulate behaviors of appetite and satiety, resulting in hyperphagia. However, alterations of the hypothalamus-adipose tissue axis in early postnatal stages have not been fully described. Analyze the short-term effect of the EPO in the hypothalamus and adipose tissue transcriptome. Overnutrition model in Wistar rats by overlactation from day 3 to day 21 of life by litter size reduction method using pup male was generated; control (n=5) and overnutrition (n=5). Transcriptome was analyzed by microarrays of expression (Ratgene ST 2.0, Affymetrix®), with a coverage of 28,407 transcripts. Quantification of glucose, cholesterol, insulin, triglycerides and leptin. The transcripts were analyzed with the cut-off points of log fold change and p-value (2, 0.05 respectively). The pathway analysis was performed with the Ingenuity Pathway Analysis soft-

ware. Bioinformatic analysis was performed on the R statistical software, statistical analysis for phenotypic and biochemical parameters were analyzed in Graphpad Prism 6® software was applied Student t probe with $p < 0.05$. The data obtained shows overweight in treatment group in 21 days of life, and high concentration of triglycerides, glucose and serum leptin. Transcriptome analysis in hypothalamus showed 98 underexpressed transcripts and 128 overexpressed. Furthermore the adipose tissue transcriptome showed 61 overexpressed and 100 underexpressed transcripts. We show for the first time the effects of EPO in the hypothalamus and adipose tissue transcriptomes to 21 days of life. EPO generates insulin resistance and dyslipidemia in the animal model. In hypothalamus deregulated pathways regulates lactation, inflammation, circadian rhythms and leptin resistance. The deregulated pathways in adipose tissue were associated to inflammation, disorder of lipid metabolism and leptin resistance.

NGF INCREASES GLUCOSE UPTAKE IN PANCREATIC β CELLS AND ADIPOSE TISSUE OF 20-DAY POSTNATAL RATS

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Around the weaning stage, in which glucose and insulin levels are high, rats show physiological resistance to insulin¹. Insulin resistance (IR) results in the disruption of the insulin signaling pathway; in which, decreases GLUT4 translocation to the membrane in adipose and muscular tissue. On the other hand, in an analysis of rats pancreatic β cell transcriptome, reported that GLUT2 is diminished in postnatal day 20 (P20) when compared with adults². This observation could be related to the decrease in insulin secretion stimulated by glucose, in animals at this age. At the weaning stage, pancreatic β cells and adipocytes are exposed to different factors that promote maturation of the cells. Among them, the change from high-fat breast milk to a high carbohydrate diet, as well as growth factors, such as nerve growth factor (NGF). Both, white adipose tissue and pancreatic β cells secrete NGF and express his receptors. This study aimed to investigate whether exposure

to NGF in β cells of Wistar rats on the postnatal day 20 promotes the translocation of GLUT2 to the plasma membrane, and establish whether glucose transport changes in this cells and also adipose tissue. From male Wistar rats of 20 days and adults, peripancreatic adipose tissue was isolated, and primary β cells cultured. We incubated β cells, and adipose tissue with NGF, and performed glucose uptake assays. We evaluated the expression of GLUT2 in pancreatic β cells, by immunofluorescence and Western Blot. After incubating the P20 cells with NGF, there was an increase in GLUT2-specific fluorescence in β cells. Moreover, we observed an increase in glucose uptake in both, pancreatic β cells and adipose tissue of 20-day postnatal rats.

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RELEVANT ROLE OF SEX IN THE MOLECULAR MECHANISM OF PHYSIOLOGICAL INSULIN RESISTANCE IN ADIPOSE TISSUE

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Insulin resistance is a condition in which the insulin-sensitive tissues cannot respond appropriately to the hormone. Adipose tissue is a crucial regulator in metabolic actions of insulin, and its dysregulation triggered this condition. Currently it has been suggested that sexual dimorphism in insulin sensitivity may be due to dimorphic differences in regulation of insulin signaling between males and females. We identified changes in the insulin signaling pathway in rat adipose tissue during postnatal development, around weaning.

We used male and female *Wistar* rats at postnatal day 20 (p20) and adult rats (Ad). We analyzed fasting glucose and insulin levels by a glucose tolerance test (GTT), and an insulin sensitivity test (ITT). We identified the phosphorylation of p-IRS-1 (Ser 1101), p-P70S6K1 (T389) and p-Akt (Ser 473) in gonadal adipose tissue, and the membrane distribution of GLUT4 in primary adipocytes. We performed insulin-stimulated glucose uptake assays in gonadal adipose tissue.

We observed that blood glucose levels in GTT in p20

male and female rats were higher than those of adults. Systemic insulin response was lower in p20 males and females rats. P70S6K phosphorylation was higher in adipose tissue at p20 in males during fasting and postprandial state, while in females it is higher only in fasting. We observed IRS phosphorylation only at p20 in males and females during fasting. Akt phosphorylation is more significant in adipose tissue of males and females at p20 during fasting and postprandial, and less GLUT 4 was observed in the membrane of adipocytes in female rats after insulin stimulation. Insulin-stimulated glucose uptake in adipose tissue was lower in p20 in males and females, compared to adults. The over-activation of the P70S6K, at this developmental stadium, activates a mechanism of down-regulation in the insulin signaling pathway in adipose tissue of p20 rats. This molecular mechanism presents sexual dimorphism.

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SUGAR, METABOLIC SYNDROME AND LOW-GRADE INFLAMMATION: AN UNSWEET COMBINATION

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White adipose tissue (WAT) is an endocrine-paracrine organ that produces many hormones called adipokines, which can be involved in insulin resistance. The cytokine profile and cells type present in WAT depends on whether adipocytes are in a lean or obese state. In the first one, an anti-inflammatory profile (Th2) predominates, with the presence of alternatively activated macrophages or M2, eosinophils, innate lymphoid cells (ILC) and regulatory T and B lymphocytes (Tregs and Bregs). In obesity, the microenvironment in WAT is pro-inflammatory (Th1), macrophages express classical activation molecules (M1), secrete pro-inflammatory cytokines, neutrophils and natural killer cells (NK) are present. The WAT inflammation is characteristic of low-grade systemic inflammation, a problem in metabolic syndrome (MS) and type 2 diabetes mellitus (T2DM).

In Mexico the incidence of MS and T2DM is high, and it is essential for public health to evaluate the common population

habits related to the incidence of MS and T2DM such as the consumption of sugary beverages. Therefore, this work evaluated the inflammatory cytokines and immune cells in the adipose tissue under a metabolic syndrome (MS) rat model, induced by 20% saccharose in drinking water administered for 2 and 6 months. The treated rats show central obesity, hypertriglyceridemia, hyperinsulinemia, mildly increased systolic pressure and insulin resistance compared to their controls.

Circulating inflammatory cytokines, like IL-1 β and TNF α , increased in all of the treated groups. In adipose tissue Tregs (TCR+FOXP3+) and M2 macrophages (F480+IL-10+) decreased, whereas M1 macrophages (F480+IL-10-) increased. This picture shows that sugar consumption can initiate a low-grade inflammation in adipose tissue that contributes to insulin resistance.

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ROLE OF ADAM 10 AND 17 IN THE RELEASE OF SOLUBLE INSULIN RECEPTOR

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Many membrane receptors have a soluble form generated by the liberation of the extracellular domain from the plasmatic membrane. The release of receptors affects the interaction between ligand-receptor, the signaling, and consequently its biological activity. The primary mechanism of soluble receptor liberation is a proteolytic cleavage by a family of enzyme called A Desintegrin and Metalloproteases (ADAMs).

We and other have previously described a Soluble form of the Insulin Receptor (SIR), which increase their levels in plasma in diabetes and metabolic syndrome. In this context, ADAM 10 and 17 have participated in the release of a variety of soluble tyrosine kinase receptors. In this work, we investigated how the activity of ADAM 10 and 17 could mediate the SIR generation.

We measure the ADAM 10 and 17 levels by immunofluorescence and western blot in adipose tissue of rats with meta-

bolic syndrome, induced by 20% sugar in the drinking water. Also, we analysed if the catalytic inhibition of both proteases participates in the SIR release in the supernatant medium of primary adipocytes culture after insulin stimulation.

We observed decrease in the immature ADAM 10 and 17 of rats with metabolic syndrome without changes in the mature form. Moreover, when we inhibited both metalloproteases, not the individual ones, we observed an attenuated SIR release after insulin stimulation, compared to controls. These results illustrate the critical role of ADAM 10 and 17 in the SIR generation in adipose tissue mediated by high insulin levels, but more experiments are needed to understand the SIR cleavage mechanism depending on this ADAMs.

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POLYMORPHISMS OF PON1 IN INFANTILE POPULATION AS AN EARLY RISK FACTOR TO DEVELOP OBESITY

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Obesity is a complex and multifactorial disease that begins in childhood and is characterized by an excess of body fat that is recognized as a health risk. Changes in the gene sequence of paraoxonase 1 (*PON1*) in obese children have been shown to be a potential marker of early development of obesity. *PON1* is an enzyme present in high density lipoproteins (HDL) with antioxidant activity, so it is attributed anti-atherogenic properties. The objective of this study was to determine the association of polymorphisms of paraoxonase 1 (*PON1*) - 108CT, Q192R and L55M in children with overweight, obesity and normal weight of Yucatán. We studied a sample of 647 children from different public primary schools in Mérida, Yucatán, stratified in 251 with obesity (OB), 85 over weight (OW) and 311 with normal weight (NW). DNA was obtained from

peripheral blood and quantitative PCR was performed for the determination of the polymorphisms. The genotypic, allelic and haplotype frequencies were determined and the most common polymorphism in the OB, OW and NW population was L55M, LL (72%, 74% and 70% respectively), L allele (84%) and the LRC haplotype (35%, 30% and 37% respectively). The genotype CT of -108CT was found as a risk to develop obesity in children OB ($p = 0.04$) but observed a protection between children OW with the genotype Q192R ($p = 0.00$) for all genotypes with dominant and over dominant inheritance studied. These results indicate the complex nature of obesity with various genetic and environmental factors, possibly influenced by the admixture of our population.

EFFECT OF EXERCISE AND ZINC ON BODY FAT ON MEXICAN ADOLESCENTS WITH METABOLIC SYNDROME

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Obesity and metabolic syndrome (MS) have been widely related. Obesity and MS treatment should include increase physical activity and reduce caloric intake. Zinc deficiency is common in people with obesity. Zn has physiological implications for metabolism, so it has been proposed as an adjunct in therapeutics of some metabolic diseases. The objective was to evaluate the effect of physical exercise and oral zinc intake on body fat percentage of adolescents with MS. A randomized clinical trial was designed; included 47 adolescents aged 15 to 18 with MS in accordance with the International diabetes federation criteria. The control Group (N = 23) performed physical aerobic exercise (60 Minutes/week) and consumed a placebo daily; the Study Group (n = 24) in addition to exercise consumed 50 mg zinc gluconate/day. The intervention was 3 months. Fat percentage was determined with a scale

mark TANITA TBF 300GS, at the beginning and at the end of the intervention. The percentage of initial-final fat and variation percentage (Δ) between men and women of both groups were compared with t-Student $P < 0.05$. Men (28.56 ± 8.64 vs 27.65 ± 8.29) and women (39.32 ± 8.5 vs 37.56 ± 8.4) treated with exercise + placebo reduced body fat at the end of treatment ($P=0.02$, $p<0.001$). Men (21.35 ± 7.7 vs 19.05 ± 6.39) and women (44.9 ± 6.41 vs 42.65 ± 6.33) treated with exercise + Zinc reduced body fat at the end of treatment ($P=0.007$, $p<0.001$). Men treated with exercise + Zinc ($\Delta-10.95 \pm 9.11$) reduced more fat compared to exercise group + placebo ($\Delta-2.79 \pm 4.15$) $p=0.039$. No differences between women ($\Delta-5.68 \pm 2.81$ vs $\Delta-4.16 \pm 3.36$, $p = 0.211$). In conclusion, exercise reduces the percentage of body fat in adolescents with SM, however, in men group zinc consumption increased fat reduction.

DIMINUTION OF THE METABOLIC RISK IN MAYA CHILDREN AFTER AN INTERVENTION WITH A NUTRITIONAL SUPPLEMENT

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The Mexican child population is facing a double burden of malnutrition, characterized by the coexistence of chronic undernutrition and besides micronutrient deficiencies, and also overweight/obesity. Malnutrition is due to the transgenerational food poverty and the indigenous areas are the most affected. Malnutrition in children leads to insulin resistance (IR) and metabolic syndrome (MetS), increasing the susceptibility to develop diabetes and cardiovascular diseases in adulthood. The aim was assess the effect of an intervention with a nutritional supplement in Maya children with malnutrition. The intervention was carried out in 29 Maya children of 9 years. Previous studies of our group in Maya's child population revealed a frequency of 50%MetS, 34.9%IR, in addition to deficiencies of essential micronutrient. The intervention was performed during a month with a nutritional supplement (code FV-UNAM), which contains vitamins, minerals, antioxidants and omega-3 fatty acids. The protocol has approval of the Human Research Ethics Committee of HJM (Hospital Juárez de México), both the parents and children signed an in-

formed consent. Biochemical, blood biometrics, anthropometry parameters were measure before and after intervention; the nutritional data were collected only during pre-intervention. Statistical analyses were performed using SPSS v21 ($P < 0.05$ significant). Data before-intervention showed that 71% of children had linear growth problems, 25% were stunted and 28% overweight/obesity. 82% had inadequate quality diet, with imbalance of macronutrients and more than 70% presented intake below the IDR of iron, calcium, vitamin A and E. 39% had metabolic risk factors, 36% excess distribution of peripheral adiposity and 17.9% had MetS. After-intervention, the children showed significant decrease in several parameters: body fat mass (4%), high blood pressure (30%), hyperglycemia (7%), hypertriglyceridemia (13%), hypercholesterolemia (7%) and hypoalbuminemia (3%). The present study demonstrated the beneficial effects in short term of nutritional intervention in Maya children. It support by DGAPA202217 Fellow CONACYT (630518).

EFFECT OF CITRUS FLAVONOIDS CONSUMPTION ON ATHEROGENIC INDEX OF RATS WITH INSULIN RESISTANCE

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Insulin resistance (IR) is a mechanism involved in the development of chronic metabolic diseases such as diabetes mellitus, hypertension, cardiovascular disease and others that increase the risk of morbidity and mortality associated with atherosclerosis.

Antioxidants have proven to be a therapeutic tool to reduce atherogenic risk. Citrus flavonoids are antioxidants derived from citrus, whose consumption has been evaluated as an adjunct in the treatment of chronic diseases.

The objective was to evaluate the atherogenic index (AI), lipid profile and reactivity of the aorta in rats with IR treated with citrus flavonoids.

Methodology. IR model was development by consumption of 30% sucrose oral, in male *Wistar* rats. Animals were divided into 3 groups: control (healthy), with IR + placebo and IR treated with 150mg/kg/day of citrus flavonoids (Hesperidin + naringenin) for one month. At the end of the treatment, ani-

mals were sacrificed, intracardiac blood was taken and thoracic aorta was dissected out. Serum lipid profile was determined by automatic methods. AI=total cholesterol/HDLc. Reactivity of the ex vivo aorta through concentration- response curves to norepinephrine (NE) and carbachol (Cch) [3.60×10^{-11} to 1.00×10^{-05} μ M].

Results. In control rats AI was 1.11 ± 0.03 , IR + placebo rats was 1.58 ± 0.09 , and IR treated with citrus flavonoids was 1.23 ± 0.05 (ANOVA, $p < 0.001$, post hoc Tukey). Citrus flavonoids reduce AI in animals with IR and have no differences with healthy animals. Citrus flavonoids reduced LDLc and total cholesterol levels. Reactivity of the Aortas exposed to NE and Cch was reduced in animals with IR treated with citrus flavonoids compared to animals with IR without treatment.

Conclusion: Citrus flavonoids reduce endothelial dysfunction and atherogenic risk associated with insulin resistance.

ASSOCIATION OF SNP RS17817449 AT FTO GENE AND ITS HAPLOTYPE (RS17817449/RS9939609) WITH OBESITY IN SCHOOL-AGED CHILDREN FROM YUCATÁN, MÉXICO

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Yucatan, México is the first place of obesity (22.7%) at the national level. Single-nucleotide polymorphisms (SNPs) rs17817449 (T>G) and rs9939609 (T>A) of the *FTO* (Fat mass and obesity associated gene) gene have been associated with obesity in children and adults. Genotypic and allelic frequencies from SNP rs17817449-*FTO*, as well as the haplotype with rs9939609-*FTO*, were determined to evaluate its association with obesity in school-aged children. Anthropometric measures were obtained: Body Mass Index percentile for age and sex (BMI_{pc}), Waist Circumference (WC) and Waist-Height index (WHI) in 303 school-aged children, 151 with obesity (BMI_{pc}>95) and 152 with adequate weight (IMC_{pc}>15<85). Buccal swab samples were obtained for genotyping the SNPs rs17817449 and rs9939609 by PCR-RFLPs. The genetic association analysis was executed with the statistical softwares SNPstats and STATA v.14.0. The three expected genotypes were found for the SNP rs17817449 (TT, GT, GG) in the studied population. The genotypic distribution was adjusted to the Hardy Weinberg expectations for school-aged children with normal weight ($p=0.16$), whereas school-aged children with

obesity was not ($p=0.0056$). The heterozygous GT genotype distribution among school-aged children with and without obesity showed significant difference ($p=0.0022$), suggesting association with lower genetic risk for obesity (OR=0.458, CI=0.281-0.747). Adjusting for gender, the SNP rs17817449 showed association with lower risk for obesity only for girls ($p=0.0048$, OR=0.352, CI= 0.171-0.725). The allelic distribution and the GG risk homozygous genotype did not show significant differences ($p>0.05$). Girls with the heterozygous GT genotype showed significantly lower mean measures of BMI_{pc} ($p=0.0195$) and ICE ($p=0.0194$). Haplotype frequency distribution (rs17817449/rs9939609) showed that the most and the least frequent combinations were T/T (60.01%) and G/A (1%) respectively. In both groups, with obesity as well as with normal weight, the most frequent combination was T/T (61.55% and 58.31%, respectively), in the studied population from Yucatán, México

Palabras clave: *FTO*, rs17817449, rs9939609, haplotype, obesity in school-aged children, Yucatan.

ASSOCIATION OF OBESITY AND ALTERATIONS IN THE FOOTPRINT WITH RISK OF FALLS IN T2DM PEOPLE

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Mexico is the second country in the world in overweight and obesity with prevalence in adults of 39% and obesity 26%; it is also the fifth with more people with type 2 diabetes mellitus (T2DM). Obesity affects the function of the foot, structurally tend to be flatter and present greater plantar soft tissue thickness. Adults with obesity have higher levels of plantar pressure, which leads to changes in the footprint, affects postural stability and changes in gait. People with T2DM have limited mobility and a decrease in strength that are factors that increase the risk of falls. This study determines the association of obesity and alterations in the footprint with the risk of falls in people with T2DM. This cross-sectional study included 37 adults (≥ 40 years and ≥ 5 years with a diagnosis of T2DM), the BMI was calculated also ranges of movement, muscle strength

(Daniels test), footprint (Hernández-Corvo protocol) and risk of falls (Tinetti). 65% presented obesity of which 68% had a high risk of falls and presented planus foot, 24% overweight with 44% high risk of falls, normal and cavus foot, and 11% normal weight with 75% high risk of falls and normal and cavus foot. There was not a significant difference between the risk of falls and the groups ($p > 0.05$).

Despite not finding a difference in the risk of falls between the groups, planus feet were only present in patients with obesity. A physiotherapeutic evaluation is required to identify the factors that contribute to the increase of gait alterations that may have implications on the risk of falls in people with T2DM.

***GSTT1* AND EXPRESSION OF MIR-222 AS A RISK FACTOR TO DEVELOP OBESITY IN YUCATECAN SCHOOLCHILDREN**

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Childhood obesity is a chronic disease that reduces the life expectancy and quality of life. In Yucatan, the prevalence of excess weight reaches 50%, exceeding the national average of 34%. The etiology is multifactorial, explained by external and internal factors. MicroRNAs explain the regulation of gene expression, where miR-222 modulates genes associated with inflammation and insulin resistance. The deletion of the gene glutathione-S-transferase (*GSTT1*) means an absence of enzymatic antioxidant activity to reactive oxygen species which increases the susceptibility to chronic inflammatory conditions. This study associates the genetic variant by deletion of the *GSTT1* gene and the levels of expression of miR-222 with characteristics of obesity in schoolchildren in Mérida, Yucatán. A case-control study was conducted; anthropometric data and peripheral blood sample were obtained for measurement of biochemical parameters, genetic analysis, genotyping *GSTT1* and expression of miR-222 by polymerase chain

reaction. For the statistical analysis, Pearson's *r* correlation, Chi-square and linear regression were performed. Data of 60 schoolchildren were analyzed (30 normal weight, 30 with obesity). The association of *GSTT1* with the nutritional diagnosis resulted in no significant difference ($p = 0.583$). The expression of miR-222 showed a significant positive correlation with creatinine levels ($p = 0.047$) and metabolic index ($p = 0.033$). The correlation of the *GSTT1* genotypes and the expression of miR-222 with other anthropometric and biochemical variables was not significant. The association by linear regression of miR-222 and Body Mass Index resulted in $R^2 = 0.013$, $p = 0.388$. No significant association was found between the genotypes of the *GSTT1* gene and the expression levels of miR-222 with obesity, with limitations in the sample size. However, the expression of miR-222 correlates significantly with creatinine levels and metabolic index.

SLEEP QUALITY AND BMI IN BED AND HAMMOCK USERS

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The association between altered sleep and body mass index (BMI) is important due to the global obesity epidemic. 72.5% of Mexican adults present either overweight or obesity and 59% of them sleep less than 7 hours per night. The purpose of this study is to compare sleep quality and the BMI between bed or hammock sleepers. 69 college students [53% female; 21 ± 1.6 years old (mean ± SD)] participated. Participants were randomized into two conditions: if they sleep in a bed ($n=33$) or in a hammock ($n=36$). The objective sleep was measured through an actigraphy device, during seven days a week, BMI was obtained with a weighing machine and altimeter

and it was applied the Epworth Scale to identify sleep habits and sleepiness (subjective sleep). Two parameters of actigraphy were significant: Activity index (ACTX) and Mean sleep episodes (MSEP). No significant differences between groups were found in subjective sleep parameters. In relation with BMI, hammock-users obtained 2.82 points above bed users ($p = 0.010$). Correlation between ACTX with BMI was significant in males that sleep in hammock ($r = 0.60$, $p < 0.01$). In conclusion, the study shows that hammock users have less punctuation in ACTX parameter and more BMI than bed users.

POLYMORPHISM OF THE GENE GLUTATHIONE TRANSFERASE THE TA 1 IN SCHOOLCHILDREN WITH OBESITY AND NORMAL WEIGHT IN MÉRIDA, YUCATÁN

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The present study was carried out with the purpose of determining the frequency of the GSTT1 genotypes in 79 school children in the city of Mérida, Yucatán, associating it with excess weight in public schools, taking into account the nutritional value of each participant. The requirements to be included in the study were that schoolchildren aged 6 to 12 years, were in a range of normal weight or obesity with the WHO BMI ranges (taking into account anthropometric measurements and deletions of the gene as the study variables). Parents were previously given letters of consent to agree or refuse to be part of the investigation. Each of the students evaluated was given a small nutrition consultation after evaluating their nutritional status through anthropometric measurements, dietary

evaluation and biochemistry. Once the blood was obtained, DNA extraction was performed in the genetic laboratory of Centro de Investigaciones Regionales Dr. Hideyo Noguchi, using the Bourne method with a change in a step instead of using sodium chloride, sodium perchlorate was used to obtain a larger condensed sample. Once the DNA samples were obtained, end-point PCR samples were made to perform electrophoresis in 1% agarose gel. The results of the research in schoolchildren were that the genotyping of the deletion of the genes of the schoolchildren did not show an association with excess weight, however there was a significant difference in the measurement of the WAIST-HIP INDEX and the WAIST-STATUTE INDEX in the minors who had the gene deletion.

THE ROLE OF PLATELETS IN TYPE 2 DIABETES PATHOGENESIS

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Type 2 diabetes is a chronic multifactorial disease involving several macro and microvascular disfunctions, as a consequence of chronic hyperglycemia. These complications could be favored by platelet count alterations, as well as functional and morphological anomalies, leading to thrombotic and cardiovascular diseases. Hyperactivation of platelets in type 2 diabetes patients increase the risk to develop cardiovascular and thrombotic events. This platelet hyperactivity could be due to an increase in sensitivity to epinephrine, ADP and trombine, as well as the presence of high levels of thromboxane and disequilibrium of magnesium and calcium ions inside the cell. Additionally, higher expression of surface adhesion molecules

as CD63, p-selectin, CD49b, CD36 and CD31 in platelet membrane and the increase in AMPc and insulin sensitivity, are the main factors contributing to increase in adhesion and platelet aggregation. Platelets have been recently considered as inflammatory immunomodulators, making them important players in chronic inflammation in type 2 diabetes pathogenesis. On the other hand, adipose tissue has been implicated in thrombus formation, so our goal was to present a model about possible alterations of platelet function involved in type 2 diabetes and its correlation with adipose tissue increase, in order to understand the role of platelets in type 2 diabetes pathogenesis.

USEFULNESS OF THE TRIGLYCERIDES/HDL-C INDEX TO IDENTIFY THE FATTY LIVER DISEASE IN PATIENTS WITH METABOLIC SYNDROME

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Fatty liver disease is a frequent complication of the metabolic syndrome and its main histopathological characteristic is the marked steatosis by triglyceride (TG) microvesicles accumulation in the hepatic parenchyma. Insulin resistance (IR) is a mainstay factor in hepatic steatosis development. Previously, the TG / HDL-C index has been used as a metabolic marker related to IR and cardiovascular risk. To evaluate the ability of the TG/HDL-C index as a metabolic marker to identify the risk of fatty liver disease in patients with metabolic syndrome. Transversal study. Patients with metabolic syndrome were included, who underwent lipids and serum lipoproteins determination. The fatty liver disease diagnosis was performed using the controlled attenuation parameter (CAP) of transient elastography (Fibroscan®), method validated, sensitive and specific for liver steatosis detection. Analysis of the receiver operative characteristic (ROC curve) was used. It was deter-

mined the sensitivity, specificity, and area under the curve (AUROC) of the TG/HDL- C index. Optimal cut-points were identified and analyzed for predictive power. Pearson correlation between the index and the value of the CAP was obtained. It was considered $p \leq 0.05$ as significant. The analysis was carried out in the statistical software SPSS® v.22. We Included 68 patients, 60.3% were men. The age average was 50.9 ± 12.1 year. The TG/HDL-C index had AUROC value of 0.78 (95% CI: 0.66-0.90, $p < 0.01$). The best index cut-off point was ≥ 3.49 with sensitivity of 70% and specificity of 94%, positive predictive value 97% and a negative predictive value of 50% for the presence of fatty liver disease. A positive correlation between the index and CAP value was found ($r = 0.437$, $p < 0.01$). The TG/HDL-C index is a simple and useful metabolic marker associated with the presence of fatty liver disease in patients with metabolic syndrome.

BARIATRIC SURGERY-ASSOCIATED DNA METHYLATION REMODELING IN ADIPOSE TISSUE FROM OBESE PATIENTS

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Obesity and its comorbidities are complex diseases where the interaction of environmental and genetic factors for their origin is required. The genetic factors identified to date only explain a small part of the variation of the body mass index (BMI). Recently it has been reported that epigenetic alterations, especially DNA methylation, may have an important role in the pathogenesis of metabolic diseases. Bariatric surgery is a radical intervention in the treatment of obesity and co-morbidities and there is still little information about epigenetic remodeling and its relation to the improved metabolic health that is associated with weight reduction after surgery. Forty one patients with obesity submitted to bariatric surgery were included. All patients were Mexicans, with similar baseline characteristics between groups, 21 with diabetes (OD) and 20 without (OB). A subcutaneous adipose tissue (SAT) biopsy was collected at the surgery time. Global DNA methylation profiles were analyzed using Illumina HumanMeth-

ylation450K Bead Chip. Methylation profiles were contrasted between groups the day of intervention and six months after. DAVID was used to enrichment analysis. We searched for differentially methylated CpG sites (DMCs) in OD, comparing with OB patients in the day of surgery. A CpG site was defined as DMC when a p value < 0.05 and at least 0.05 absolute mean methylation difference. Six months after the surgery, a SAT biopsy was collected for all patients. DNA methylation profiles were evaluated and compared with those at the moment of surgery. We found diverse DMCs in OD compared with OB patients at the time of surgery. Analysis of DNA methylation after 6 months of surgery, showed changes in profiles in both OD and OB patients. Many of DMCs reversed their differences between both groups. We also found sites with a high correlation between DNA methylation level and clinical parameters.