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Diabesity among the Yucatecan Maya: Metabolism, genotype, phenotype and considerations of the sociocultural environment and early development

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RESUMEN

Diabesidad en los mayas de Yucatán: Metabolismo, genotipo, fenotipo y consideraciones del ambiente sociocultural y desarrollo temprano.

La diabesidad es un neologismo que nosotros utilizamos para describir a la diabetes tipo 2 en un contexto de obesidad. En esta revisión descriptiva, nuestro objetivo fue analizar el fenómeno de la diabesidad contextualizada en la población maya yucateca, dada la importancia demográfica de esta etnia en el país y por la alta prevalencia de diabetes y obesidad. Primero describimos los rasgos fenotípicos y genotípicos asociados con la diabesidad; también discutimos el papel de los factores socioculturales que han incidido en el patrón alimentario de los mayas y la evidencia disponible respecto a las características fenotípicas adquiridas durante las primeras etapas de desarrollo y sus posibles repercusiones en el metabolismo y la presencia de obesidad y diabetes. Finalmente, proponemos que la falla en la secreción de insulina y la glucolipotoxicidad son factores comunes y un posible factor unificador de la diabesidad entre la población maya. Para ello recurrimos a fuentes primarias de información, incluyendo artículos originales de investigación y capítulos de libros editados sobre diabesidad y ensayos sociohistóricos sobre la población maya.

ABSTRACT

Diabesity is a neologism that we use to describe Type 2 diabetes in the context of obesity. In this descriptive review, we aim to analyze the phenomenon of diabesity in the context of the Yucatecan Maya population, given the demographic importance of this ethnic group in Mexico and due to the high prevalence of diabetes and obesity observed.

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Firstly, we describe the phenotypic and genotypic traits associated with diabesity. We also discuss the role of the sociocultural factors that have impacted the dietary pattern of the Maya, the available evidence regarding the phenotypic characteristics acquired during the early stages of development, their possible repercussions on the metabolism and the presence of obesity and diabetes. Finally, we propose that the failure of insulin secretion and glucolipotoxicity are common factors and a possible unifying factor of diabesity within the Maya population. For this purpose, we draw upon primary sources of information, including original research articles, chapters from edited books about diabesity and sociohistorical essays on the Maya population.

INTRODUCTION

In recent decades, type 2 diabetes (T2D) has ranked among the main chronic non-communicable diseases in many countries, with obesity as an important factor in its etiology (1). In Mexico, the Amerindian component plays an important role in the configuration of this phenomenon and has been associated with two factors: genetic susceptibility and hyperinsulinemia (2).

Due to the high coexistence of diabetes and obesity and their interrelation in their physiopathologies, this phenomenon has been named diabesity (3). Studies have focused on describing the combined effects of diabetes and obesity and their treatment. Therefore, it is necessary to use a comprehensive theoretical framework that contributes to understand the phenomenon of diabesity. From evolutionary and biocultural perspectives, sociocultural factors interact with the genetic component of individuals, shaping metabolism in specific ecological contexts. This complex interaction can predispose the individuals to a failure in insulin secretion, which may be exacerbated by insulin resistance and the accumulation of lipids in places other than just the adipose tissue (lipotoxicity) (4).

The ethnic groups of Mexico have historically lived in poverty. Recent changes in their productive systems have exposed the individuals to scenarios that increase the risks for chronic degenerative diseases. In this article, we analyze the phenomenon of diabesity in the context of the Yucatecan Mayans, given the demographic importance of this ethnic group in the country and due to the high prevalence of T2D and obesity in rural and urban contexts.

In this paper, we aim to 1) describe the phenotypic and genotypic traits associated with diabesity, 2) discuss the role of the sociocultural and early-life environment in the development of this phenomenon among the Yucatecan Maya, and 3) propose a possible unifying factor of diabesity in the Maya population. For this purpose, we draw upon primary sources of information, including original research articles about the etiology and physiopathology of diabesity, chapters from specialized books about the human biology of the Yucatan Peninsula, and classical sociohistorical essays on the Maya population.

1. Diabesity: a neologism beyond diabetes and obesity in the Mayan population.

The term “diabesity” was coined to describe the coexistence of the diabetes and obesity epidemics (3). However, the term can be used to reflect more deeply on the causes and development of the phenomenon (5). In this review, we use it as a neologism to refer to diabetes that occurs when a set of genes predispose a dysfunction of the beta-cells of the pancreas and interact with genes related to resistance to insulin and obesity in a sociocultural context that enhances the disease.

Due to the strong coexistence of these pathologies, it has been suggested that there are biological links and sociocultural conditions that interact in particular ecological contexts (3). From an evolutionary perspective, the link that unites both pathologies is insulin resistance. This perspective proposes that natural selection operates through metabolic pathways regulated by genes or a set of genes. These have conferred advantages to the individuals of our species in terms of the efficient use of energy to cope with the numerous physiological processes, including maintenance and reproduction in environmental contexts with limited food resources (5). In recent years, research

has shown the role that certain genes play in the relationship between diabetes and obesity in the Mayan population. Whilst the *FTO* (6-9) gene has been less frequently associated with obesity, the *ABCA1, CDKN2A/2B, WFS1* and *SIRT1* genes have been more frequently related to decreased insulin secretion, and the *PPP1RA* and *AGTR2* genes to the deficient action of insulin.

During the last five centuries, the Maya have lived in poverty. In recent decades, the nutritional ecology of this ethnic group has been transformed substantially, particularly in terms of the worsening of their diet and a decrease in the levels of physical activity. These conditions have contributed to the coexistence of chronic undernutrition and overweight/obesity (10). Table 1 shows the anthropometric and body composition characteristics of a sample of adult Maya women residing in urban areas of Yucatan who participated in a recent study (10). The women show very low statures and high values for body mass index (BMI), waist circumference, and percentage of body fat. The waist circumference values show a clear trend towards the accumulation of body fat in the abdominal region and a high prevalence of abdominal obesity.

Table 1. Anthropometric and body composition characteristics in a sample of Maya women from Yucatan, by age groups.

Variable	40-49 years n = 34		50-59 years n = 100		60-69 years n = 95		70-79 years n = 31	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Height (cm)	144.99	4.95	143.66	4.89	141.99	4.42	140.16	4.67
Weight (kg)	69.45	11.82	66.22	11.82	65.14	11.63	60.36	9.07
BMI (kg/m^2)	33.03	5.42	32.02	5.07	32.23	5.14	30.71	4.38
WC (cm)	96.95	9.41	97.98	9.89	98.58	11.42	96.50	7.75
BF (%)	48.74	5.04	50.48	4.58	53.41	4.75	54.84	5.42

BMI: body mass index; WC: waist circumference; BF: body fat.

Compared with other Mexican ethnic groups, the Maya have the highest levels of T2D (6). It seems that the prevalence of diabetes among the Maya has grown substantially in the last three decades of the twentieth century and the first decade of the present century. The increase of T2D in this population has been accompanied by a much higher rate of increase in obesity rates (11).

1.1 Factors associated with diabesity in the Maya population.

1.1.1 The Ancestral Amerindian component among the Yucatecan Maya

The Maya is the largest ethnic group in America and the second largest ethnic group in Mexico. In 2020 in the state of Yucatán, the number of Maya-speaking people was 519,667 (12). Several biocultural traits characterize the Maya. On the one hand, they have some genetic characteristics with the same structure as the Native American population and distinctive traits that correlate with the native population of the Yucatan Peninsula. These characteristics are the result of an evolutionary history in a region whose physiographic characteristics limited the movement of populations to an inhospitable environment during the late Pleistocene and early Holocene (between 13,000- and 7,600-years BP) (13). On the other hand, contemporary Maya show high levels of poverty and marginalization that have their origin in three centuries of Spanish domination during the colonization as well as the national and regional policies of independent Mexico that have kept this population under adverse socioeconomic conditions (14-16). These characteristics and conditions appear to have shaped not only a particular phenotype but also a complex epidemiological profile.

1.1.2 Abdominal obesity and insulin resistance

Evidence shows that the genetic factors linking abdominal obesity and insulin resistance/sensitivity in the Mayan population are associated with the *FTO*, *AGTR2*, and *PPP1R3A* genes.

In particular, the *FTO* gene has been related to increased energy intake from fat or protein, increased appetite, and reduced satiety in several populations (17-19). In the Maya, it has been associated with weight, BMI and waist circumference of children with a high Mayan component (9).

Additionally, in a pilot study of exomes, the *AGTR2* gene has been associated with T2D in the Mayan population (7). This gene is an angiotensin II receptor that has been related to the modulation of insulin sensitivity (20) and has been proposed as a therapeutic target in glycemic control in patients with T2D (21). Finally, the *PPP1R3A* gene related to insulin resistance in the Mayan population has been associated with high levels of *HOMA-IR* (8). This gene has been related to insulin resistance and T2D, since alterations in the protein phosphatase 1 subunit, encoded by this gene, lead to weight gain, fat deposition and the development of insulin resistance (22).

Adipose tissue has been considered a tissue with specific characteristics, including a metabolically dynamic endocrine organ, which in addition to being the main place of energy storage, is capable of synthesizing a series of biologically active compounds (adipokines) that regulate a variety of processes such as control of energy intake (leptin, angiotensin), control of insulin sensitivity and mediators of the inflammatory process (tumor necrosis factor **α** [TNF-**α**], interleukin-6 [IL-6], resistin, visfatin, adiponectin, among others). These adipokines are critical in the regulation of glucose homeostasis and insulin signalling. Thus, impaired production of these hormones correlates with the development and progression of T2D.

Additionally, the distribution of adipose tissue in the body is decisive in the regulation of insulin sensitivity. Even in people with a healthy weight, those with a more peripheral distribution of adipose tissue are more sensitive to insulin than those with a predominantly central distribution of adipose tissue, that is, in the abdominal and thoracic region. The causes of this difference are diverse; intra-abdominal fat expresses more genes that encode secretory proteins and proteins responsible for energy production through receptors that activate AMPK (23).

1.1.3 Dysfunction of beta-cells.

Research has found that the *ABCA1, CDKN2A/2B, WFS1*, and *SIRT1* genes are related to beta-cell dysfunction in the Maya. In 2015, we found a relationship between the rs9282541 variant of the *ABCA1* gene and T2D. Interestingly, we found that carriers of the T allele decrease the functionality of the beta-cell, measured by a *HOMA-B* calculation, which suggests low insulin secretion in individuals carrying this allele (6).

The *CDKN2A/B* gene participates in the proliferation and regeneration of beta-cells by coding for two inhibitory proteins known as cyclin-dependent kinases (CDK), p16INK4A and p15INK4B. These prevent the activation of CDK4/6 by D-cyclins, thus blocking cell cycle entry (24). In 2015, we evaluated the rs10811661 polymorphism, finding it associated with T2D in a Maya sample.

The relationship between the *WFS1* gene and the risk of T2D has only been documented in a pilot exome study in the Mayan population. Therefore, its implication in the pathophysiology of T2D in this population should be analyzed in the future. In this pilot study, the association between the *SIRT1* gene and diabetes was verified. This gene codes for a set of intracellular regulatory proteins with mono-ADP-ribosyltransferase activity (7).

1.1.4. The Metabolic biochemical phenotype in Diabesity.

Given the importance of insulin resistance and its key biological role in diabesity, it is important to measure or estimate it indirectly as it is an important element in the metabolic assessment of patients with diabesity. Taking into account the context in which indigenous communities live, the indirect estimation of insulin resistance turns out to be a practical approach. There are currently several indices that

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indirectly measure insulin resistance, such as the metabolic index. This has been shown to have a good prognostic value, as it incorporates the strength of the detection of atherogenic dyslipidemia by the Triglycerides/HDL-C ratio and the concentrations of glucose, which in a fasting state, together with triglycerides, represents a good estimate of hepatic insulin resistance (25). We have studied this index in the diabetic Maya population, where abdominal obesity, hypertension and insulin resistance were characteristic. The index was associated with increased cholesterol levels, specifically after 5 years of progression, opening an opportunity for its use as a good estimator of atherogenic risk (26).

1.1.5 "Diabesitogenes" in the Mayan population.

Defects in both insulin secretion and action appear to be inherited. The heritability of these defects has been studied by comparing the offspring of individuals with a deficient insulin secretion phenotype with the offspring of individuals with a resistant phenotype to insulin. The offspring of those with a deficient insulin secretion phenotype had impaired insulin secretion capacity but normal insulin action, whilst the offspring of individuals with a resistant phenotype to insulin had impaired insulin action but normal insulin secretion capacity (27). This phenomenon denotes that the pathophysiology of diabetes and obesity is multifactorial and polygenic. The ever-increasing efforts in the search for specific genes, such as exome analysis, have allowed us to identify certain genes related to both beta-cell dysfunction and insulin resistance. However, we have not been able to identify a specific gene related to beta-cell dysfunction and insulin resistance in isolation. This has led us to the same point where we cannot identify what occurs first in the pathophysiology of T2D, and we continue to ask ourselves: is it the failure or dysfunction of the beta-cells, or is it insulin resistance? A large part of this dilemma is, perhaps, the approach of wanting to identify the primary defect. Therefore, an integrative research approach could help us to understand how the phenomenon of "diabesity" develops (28).

Some variants of the *FTO* (rs9939609) and *ABCA1* (rs9282541) genes have been studied to explore their interaction and effect on BMI and waist circumference in adults. It was found that when both risk variants are present, they are not related to BMI or waist circumference. However, when the *FTO* risk variant is present in the absence of the *ABCA1* risk variant, the *FTO* gene is strongly associated with BMI and marginally associated with waist circumference, as seen in European populations. Although *FTO* and *ABCA1* are known to be important in adipose tissue function (29-30), there is no experimental evidence to date of the functional link between both genes. However, *ABCA1* has shown an important relationship both with the distribution of body fat in the Mexican population (31), and with the waist-hip ratio in various populations (32). The *ABCA1-FTO* interaction study shows the importance of the Native American component as a result of adaptive processes related to energy saving, as the *ABCA1* gene variant is exclusive to American populations (33). This study also shows the importance of the combination of specific alleles that have resulted from miscegenation in the Mexican population.

It is possible that beta-cell dysfunction is the main risk factor for the onset and progression of T2D as this dysfunction has been related to obesity through elevated concentrations of circulating fatty acids and alterations in the regulation of lipid metabolism. The chronic increase in fatty acid concentrations leads to a state of lipotoxicity and the apoptosis of beta-cells, altering their mass and initiating a vicious circle that leads to their dysfunction (34).

Based on the aforementioned, we propose that this group of genes and their interactions be called "diabesitogenes". We think that the different combinations of genes related to the T2D-obesity dyad can manifest themselves differently in populations, groups of individuals or even in families, not just based on their evolutionary history but also on the particularities of their recently experienced sociocultural changes.

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2. Historical poverty and recent changes in sociocultural systems and their impact on the nutrition of the Mayas.

The history of the Maya is characterized by secular poverty. During the colonial period, the Spaniards established a sociopolitical domination based on a system of tribute, tax payment, and forced labor. During this period, the Maya were also affected by several episodes of epidemics (35, 36). The epidemic-famine dyad was repeated on numerous occasions. The mortality and morbidity reduced the labor force necessary for agriculture and the decimated nutritional status and chronic hunger of the Maya. Between the second half of the nineteenth century and the first half of the twentieth century the henequen haciendas required a large number of workers (37). The Maya experienced miserable conditions on the haciendas. Working shifts for the Maya in the haciendas consisted of approximately 12 hours of very demanding physical activities (38). During most of the twentieth century, there were significantly higher poverty rates due to the unemployment caused by the collapse of the henequen system (16). In summary, the history of the Maya during the last centuries is a history of poverty, marginalization and labor exploitation. The transgenerational inertia of poverty experienced by the Maya during recent decades is explained by the limited opportunity and access to education and decent working conditions. From the second half of the past century to the present, the Maya have experienced important changes in their socioeconomic dynamics. By 1950, a process of migration to the main urban centers of Yucatan began, which would intensify by 1970 with the specialization of a service-based economy. For the Maya, this not only implied a change of residence, but a profound transformation of their lifestyle (16). Another group has remained in their places of origin, facilitating tourist activities as small service providers, and in other cases, as employees in the Mexican Caribbean (39). Some have found employment in the *maquiladoras* that have sought low-cost labor in some municipalities of the state. In parallel, the rural Maya have gradually undergone a transition from agricultural production for self-consumption to small-scale commercial agriculture (40). These factors, together with the globalization of the markets, contributed to a substantial reduction in the food supply from the traditional production system and a consequent change in their dietary patterns (41). Although these processes have had regionally differentiated effects in Yucatan, as a whole, they have exposed the Maya to global consumption patterns. Salaried jobs have allowed families - even those in socioeconomically disadvantaged conditions, to include high, energy-dense and nutritionally poor products into their diet, resulting in a low intake of vitamins, minerals and fiber (42). These changes have had an important effect on the body composition of individuals, with substantial increases in obesity in those residing urban contexts (43).

In summary, the Maya face a double-edged sword. On the one hand, regardless of the geographical context they occupy, their levels of poverty are higher than those of the non-Maya population. On the other hand, as a result of global processes, the Maya have shown substantial changes in their consumption patterns, a situation that exacerbates the deterioration in the nutritional status of individuals. The double edge of this sword has shaped the current epidemiological panorama of the Yucatecan Maya.

2.1 Early development and intergenerational influences shaping the Maya phenotype.

The studies have shown the importance of the environment experienced during the early stages of ontogeny (the first 1,000 days of life) on the health during adultness. Under adverse conditions (e.g. nutritional deficit), developing organisms undergo permanent structural and physiological adjustments that allow them, in the short term, to survive and reproduce (44). These adjustments have been called developmental or fetal programming and more recently, phenotypic induction (44). Later, during adultness, in the presence of nutritional transition, the fetal structural and functional adjustments play an important role in the development of metabolic abnormalities including T2D and dyslipidemias.

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Several mechanisms may explain how fetal programming can occur during intrauterine development. The most important is the alteration of normal tissue and organ development. Maternal undernutrition may impact offspring organ size or function (45). Evidence for such organ alteration has been studied most thoroughly in the kidney and pancreas. In humans, the number of nephrons is reduced in patients with primary hypertension (46) and low birth weight has been associated with reduced renal volume, which may indicate a reduced number of nephrons (47). T2D is also shaped by nutritional programming. A low-protein diet given to rats and mice during gestation induces a reduction in the number of functional beta-cells of the pancreas (48). The second mechanism is the disruption of the endocrine environment during gestation including the increased levels of both maternal and fetal glucocorticoids and permanent changes in the homeostatic regulatory control of metabolic pathways (49). The impact of maternal nutrition on fetal programming can also be explained by changes in the epigenetic code. During gestation, the developing embryo/fetus is particularly susceptible to epigenetic changes that may shape life-long effects on the phenotype, function and the presence of metabolic abnormalities. Studies with sheep subjected to a diet deficient in methyl donors, folic acid, vitamin B12 and methionine during preconception and early gestation were associated with insulin resistance and elevated blood pressure in male offspring (50).

Low birth weights have been linked to higher blood pressure (51), cholesterol (52), diabetes and adiposity (53) during postnatal life. Azcorra *et al.* (2016) (54), showed that Yucatecan infants born during 2013 whose mothers have two Mayan surnames had birthweights (3088 g) lower than those born to women with one Mayan surname (3106 g), and even lower than newborns of women without Mayan surnames (3150 g). Subsequently, Azcorra and Méndez (2018) (55) reported the impact of maternal height on the birthweight of Maya infants from Merida; infants born to mothers in the lowest quartile for height (129-147 cm) had 0.5 standard deviations less for birthweight compared to infants born to mothers in the highest quartile for height (156-180 cm). The Yucatecan Maya show the shortest heights in the global adult population as a result of chronic undernutrition during childhood. Also, birth weight has been positively associated with fat and fat-free mass in Maya children at 6-8 years of age (56). The phenotypic characteristics acquired early in development appear to be transmitted intergenerationally through epigenetic processes. Some studies have shown that individuals with short stature have a higher risk for adiposity (57,58) which seem to be explained by alterations in metabolism and appetite regulation. As a whole, these are considered physiological adjustments that have repercussions on metabolic pathways that contribute to shaping the phenotype from early life (5). In theory, these adjustments can be transmitted from mother to fetus, Azcorra *et al* (59) showed an inverse association between maternal height and the levels of total body fat, waist circumference and skinfolds in male Maya children. That is, the amount of body fat in children increased as their mothers were shorter. These results suggest that maternal nutritional history contributes to shaping the body composition of their children.

3. Failure in the secretion of insulin and glucolipotoxicity: Common elements of diabesity in the Mayan population.

This review shows that the complex interaction between the genetic component and the environment and the consequent high frequency of diabesity in the Maya population may have common elements. We hypothesize that the main element is a failure in the secretion of insulin by beta-cells, which is exacerbated by the glucolipotoxicity generated by abdominal obesity and insulin resistance.

In terms of population, a set of genes (diabesitogenes) is inherited that predispose or increase the risk of T2D, obesity and resistance to insulin. These genes interact with sociocultural factors (dietetic and physical activity patterns), early development and maternal capital that exert a differentiated influence at each stage of individuals'

lives. Alterations in the regulation of lipid and carbohydrate metabolism in these contexts are toxic to cells; this scenario also underlies the interaction with "diabesitogenes" related to functional and structural alterations of the beta-cell of the pancreas.

Furthermore, it is known that insulin acts on the hypothalamus, repressing anabolic circuits, which stimulate food intake and inhibit energy expenditure, having a direct effect on body weight. Therefore, the decrease in the release of insulin can affect metabolic homeostasis (60) at the level of the central nervous system. Against this background, it is believed that a relative reduction in insulin release results in decreased insulin action in the hypothalamus and is associated with weight gain, and thus may contribute to increased insulin resistance.

Studies in mice and humans have documented that insulin resistance at the beta-cell level could play a role in the pathogenesis of defective insulin release (61, 62). Although both insulin resistance and reduced insulin secretion are involved in the pathogenesis of diabesity, the common elements appear to be different in various ethnic groups (Figure 1).

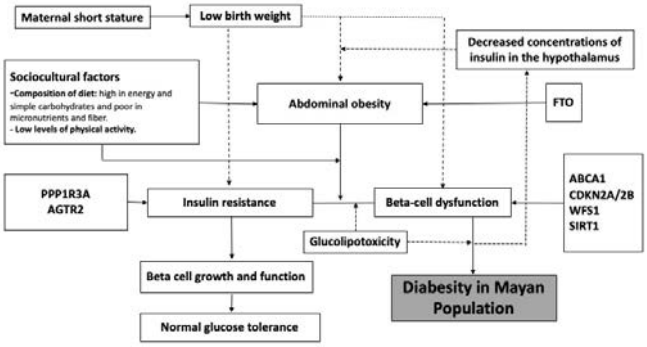

Figure 1. Model of the interaction between genetic, ontogenic and sociocultural factors that shape diabesity in the Yucatec Maya population. The continuous lines represent the current evidence in the Mayan population and the dashed lines the evidence available for other populations (63).

FINAL COMMENTS

Diabesity is highly frequent among the Maya. The causes of this phenomenon are diverse and complex. A set of genetic characteristics most likely acquired at the beginning of the settlement of America associated with the metabolism of carbohydrates and lipids seem to generate the biological bases of the phenomenon. These genes were selected by evolution because they conferred advantages to cope with reproduction, growth and immunological competence in an ecological context with limited resources.

Recent events appear to have exacerbated the phenotype and biochemical expression of such genetic characteristics. The conditions experienced during the colonial period played an important role in the deterioration of the biological status of the Maya through poverty that, along with continual epidemics, caused high rates of chronic undernutrition. Along with these conditions, continual epidemics and gene flow may have also contributed. Such conditions may have caused metabolic adjustments during early development, leading to energy saving strategies.

More recently, abrupt changes in sociocultural systems related to the production, distribution, supply, selection and preparation of food have led to a deterioration in the nutritional quality of the traditional Maya diet. This fact has generated dietary patterns characterized by excessive energy intake and poor consumption of micronutrients. Overall, these processes have shaped the recent somatic and metabolic biochemical phenotype of the Maya and their epidemiological profile (Figure 2).

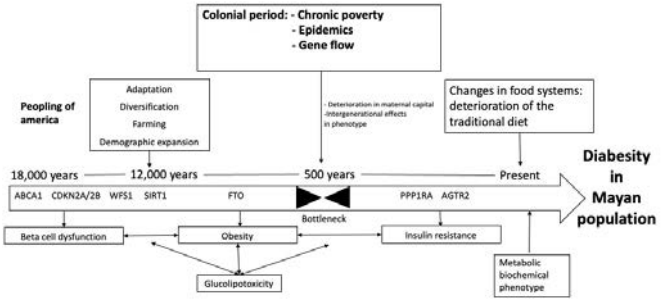

Figure 2. Schematic representation of evolutionary and socio-historic factors that interact in the configuration of diabesity phenomenon in the Yucatec Maya population.

The concept of diabesity allows us to discuss the mutual causes that interact and lead to insulin resistance and deficient insulin secretion,

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orchestrated upon a complex pathophysiology and particular environmental context which supports both phenomena. This allows us to visualize diabesity under the magnifying glass of evolution.

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