Curr Obes Rep (2015) 4:92–98
DOI 10.1007/s13679-014-0132-9

PSYCHOLOGICAL ISSUES (M HETHERINGTON AND V DRAPEAU, SECTION EDITORS)

High-Risk Populations: The Pimas of Arizona and Mexico

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Published online: 21 January 2015

Abstract The purpose of this review is first, to broadly summarize the long-term commitment that began in 1965 to studying type 2 diabetes and obesity through the cooperation of the Pima Indians of Arizona, and second, to discuss the investigations with the Pima Indians of Mexico that started in 1991. The later studies emphasize gene-environment interactions in the pathogenesis of these metabolic disorders. Through the participation of both groups of Pimas, the researchers made key findings with regard to the epidemiology, physiology, clinical assessment and genetics of type 2 diabetes and obesity.

Keywords Type 2 diabetes · Pima Indians, Arizona · Pima Indians, Mexico · Obesity · Genetics · Lifestyle · Environment

Introduction

The Pima Indians of Arizona and Mexico have contributed to numerous scientific gains through their willingness to participate in the research process. Their involvement has led to significant findings with regard to the epidemiology, physiology, clinical assessment, and genetics of both type 2 diabetes and obesity. Longitudinal investigations, starting in 1965, have involved study participants living on the Gila River Reservation outside Phoenix, Arizona and, since 1991, the residents of the community of Maycoba, Mexico.

The purpose of this review is broadly to summarize the contributions to our current knowledge resulting from the participation of the Pimas in both countries. It starts with the original documentation of the epidemic of diabetes and obesity among the Pimas of Arizona and proceeds to the developing concerns for their genetically-related counterparts in Mexico.

Historical Perspective

The *O'odham* (Arizona), *O'ob* also *Pima Bajo* (Mexico) [1], or Pima in general, are descendants of the ancient *Hohokam*, who have inhabited the Sonoran desert and Sierra Madre regions for centuries [2]. About 300 B.C. the *Hohokam* moved into the Gila River valley, at that time still Mexican territory [3]. After the United States acquired parts of northern Mexico in the 1853 Gadsden Purchase, the *O'odham* and the *Pima Bajo* became further separated and, ultimately, had little future contact. In 1959 a Pima reservation in Arizona was created and the majority of Arizona Pima continue to reside there [2].

The Pimas of Arizona adapted to their desert homeland by directing water through an elaborate system of irrigation canals to support subsistence agriculture; they grew corn, beans, squash and cotton [4]. Sadly, around 1900 the increased population of white settlers to the north led to the eventual diversion of the water that supported the Pimas' way of life [5].

The forced curtailment of farming led to significant impacts on their food intake, physical activity and their economy [6]. Their life changed from farming sustained though physical labor to one of food scarcity and little labor. Famine, rarely experienced in the past, became chronic. As a result, this time period marked the end of a lifestyle to which the Pima were well-adapted and transitioned to a lifestyle for which they were poorly adapted. Their low-fat, high-carbohydrate diet

This article is part of the Topical Collection on *Psychological Issues*

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changed to one that ultimately derived more than 40 % of its energy from fat [7]. At the same time the demand for physical labor subsided.

The timing of this significant change in lifestyle and livelihood coincides with the development of diabetes among the Arizona Pimas. At the turn of the nineteenth century, Hrdlicka recorded one case on the Gila River Reservation [8]. In 1937, Joslin documented 21 persons with diabetes there and concluded that the presence of diabetes among the Pimas was similar to that of the general U.S. population [9]. By the 1950s, however, the prevalence had increased tenfold [10], and a study initiated in 1965 documented in the Arizona Pima Indians the highest prevalence of diabetes ever recorded [11].

The onset of this epidemic stimulated a longitudinal study initiated at the Sacaton Service Unit of the Indian Health Services. Residents of the Gila River Indian Reservation, regardless of health status, who were of at least half Pima ancestry and age five and older, were invited to participate. Each volunteer was examined approximately every two years. The examinations included a medical history, physical examination, medical record review and oral glucose tolerance test [12].

Using ten years of this longitudinal data (periodic glucose tolerance testing and medical record reviews) a comparison of diabetes prevalence and incidence was assembled between the Arizona Pimas and the predominantly White population of Rochester, Minnesota. The results indicated that the Pima had a 19-fold greater incidence of diabetes than the sample population in Rochester [12]. Although it was already known that Native heritage is associated with higher diabetes prevalence [13], the situation with the Pima was unique.

The frequency of type 2 diabetes has continued to increase. By 1970, the prevalence of type 2 diabetes was about 40 % among Pimas age 35 and older, and currently affects about half of all Pimas over age 35 [14]. By the mid-1970s, the Pima were also more obese than similarly aged Caucasians [5]. Studies supporting the familial nature of diabetes and obesity among the Pimas indicated a clear genetic component to these disorders [5]. But how would a propensity for the development of type 2 diabetes and obesity accommodate the "survival of the fittest" explanation of genetic selection?

The "Thrifty gene" Hypothesis

A mechanism was put forth by Neel in 1962—the "thrifty gene" hypothesis [15]. Neel proposed that in the past, populations who have struggled with periods of limited resources and therefore, have experienced periods of famine, were more likely to survive if they were metabolically thrifty and stored calories efficiently. Their survival gave a genetic advantage to this characteristic. Based on his hypothesis, however, what had been historically an advantage became detrimental as time elapsed. Through modernization food has become abundant and continually available. The genetic capacity to store calories efficiently in our current environment becomes a risk factor for type 2 diabetes and obesity.

The Pima Indians of Arizona represent a living example of such a transition from a traditional lifestyle with limited food supply and high physical activity to a modern, sedentary lifestyle with a consistent food supply [6]. During and following this transition the prevalence of type 2 diabetes and obesity soared to crisis proportions. Such a change in environment has been very costly to the health of the Pimas.

Longitudinal studies of the Arizona Pimas have supported the "thrifty gene" hypothesis. Bogardus and Ravussin [14, 16] demonstrated that both resting metabolic rate and 24-hour energy expenditure aggregate in Pima families. They also documented a large variability in resting metabolic rate at any given body weight and composition that is not accounted for by intra-individual variability [14]. Therefore, individuals with similar physical characteristics can require more or less energy to maintain their body weights. Furthermore, the familial dependence of the resting metabolic rate is a contributing mechanism to the familial predisposition toward obesity [14]. Thus, the link between weight gain and resting metabolic rate can be viewed as a regulatory mechanism to compensate for a genetically "thrifty metabolism."

The Mexican Pimas

In addition to the Pimas in the United States, another group of Pimas lives in the Sierra Madre Mountains around the small town of Maycoba in the Mexican state of Sonora. Until 1991, the only access to this region was an arduous drive from Hermosillo and included a harrowing crossing of a rope bridge. In spring, however, a series of dramatic paved switchbacks were constructed through the 1600-km-long spine of the Sierra Madre mountains. They have made Maycoba and the surrounding communities far more accessible [17].

At that time, the Mexican Pima were living a subsistence lifestyle [18]. They grew the majority of their own food on sloped fields called maguechis that are labor-intensive to maintain. Their homes had no running water or electricity and therefore food preparation and household chores required considerable effort [19]. This contrast in lifestyle between the two groups of Pimas presented a significant opportunity to compare disease prevalence between the Arizona Pima, who live a largely modern lifestyle characterized by high dietary fat intake and sedentary lifestyle, and the Mexican Pima, who had not experienced abrupt environmental changes affecting their way of life and in whom the diabetes prevalence was unknown [19].

Thus, we began the inaugural visit to Maycoba in 1991 for a pilot study by a group of scientists from both Mexico and the United States, unannounced to the community, but fortunately well-accepted. Upon arrival in Maycoba, we sought the assistance of local health professionals and set up laboratory and anthropometric stations in the yard in front of the

neighborhood clinic. Local people were asked if they were Pima and willing to participate; thirty-five individuals volunteered [19]. We obtained consent by explaining to the participants that we wanted to learn from them in order to help their relatives to the north.

Nineteen women and 16 men underwent measurements of weight, height, body fat, blood pressure, plasma levels of glucose, cholesterol, and HbA1c. These values were then compared with sex-, age-, and diabetes-status matched Pimas living in Arizona. Mexican Pimas were lighter and shorter with lower body mass indexes and lower plasma total cholesterol levels than Arizona Pimas. Only two women (11 %) and one man (6 %) had type 2 diabetes, contrasting with the expected prevalence of 37 % and 54 % in female and male Arizona Pimas, respectively [19].

As a result of this dramatic difference in diabetes prevalence a more far-reaching study was initiated [20]. The long-term commitment to studying disease patterns in the Pima Indians of Arizona provided an excellent opportunity to examine etiological factors by comparison with a group of Pimas living under markedly contrasting conditions in Mexico. Since the Mexican Pima population had not experienced many of the abrupt changes in environmental conditions that paralleled the emergence of type 2 diabetes and obesity in the US Pima community, we hypothesized that the prevalence of these two disorders would be lower.

An additional opportunity was provided by a group of people who reside in Maycoba with no Pima heritage. Theoretically, they would not be genetically predisposed to type 2 diabetes and obesity. It was therefore possible to compare diabetes and obesity prevalence in two genetically-related populations living in different environments (Arizona and Mexican Pimas) and two groups living in the same environment but not genetically related (Mexican Pimas and non-Pima Mexicans).

The larger study began in 1994 with a census of Maycoba and surrounding communities to determine various demographics of the population including the ethnicity, familial relationships, and individuals' ages. Ethnicity was determined similarly to the Arizona Pima studies; participants were marked as full-Pima if both parents were reported to be full Pima, and part-Pima if one parent was reported as Pima. Most importantly, a genetic analysis was conducted and concluded that Arizona and Mexican Pimas are closely related and share a similar gene pool [20].

Residents of the community were individually asked to take part in the study, which included a health exam at the research clinic established in a small community outside the town of Maycoba. For reasons of comparison the same measures and methods were used as in the Arizona studies and included a medical history, 24-hour dietary recall, physical activity survey, blood pressure and anthropometric measurements, and a 75-gram oral glucose tolerance test.

The major findings of this work were: a) the age- and sex-adjusted prevalence of type 2 diabetes in the Mexican Pima Indians (6.9 %) was less than one-fifth that in the Arizona Pima (38 %); b) the prevalence of type 2 diabetes in Mexican Pimas (6.9 %) was not significantly different from the non-Pima Mexicans (2.6 %); c) the prevalence of obesity in Mexican Pimas (9 % in men, 27 % in women) was dramatically lower than the Arizona Pimas (64 % in men, 75 % in women); and d) the prevalence of obesity was similar in Mexican Pima Indians (9 % in men, and 27 % in women) and non-Pima Mexicans (7 % in men, 20 % in women) [20].

The physical activity results indicated that Mexican Pima and non-Pima Mexican men and women shared similar moderate to heavy occupational activity, as well as leisure activity levels. However, both Mexican groups had significantly higher physical activity levels than the Arizona Pima population, independent of sex and age. The levels of moderate to heavy physical activity were approximately 2.5 times greater among Mexican men and seven times greater in Mexican women when compared to the Arizona Pima counterparts [20].

Dietary differences within and between the two communities were also noted. There were no significant differences in energy intake between both Mexican groups (Pima and non-Pima), but it was higher in men than in women. The diet of both Mexican groups consisted of a very low percentage of calories derived from fat with an average of twenty-five percent. The amount of dietary fiber was greater than 50 g/day and similar in both groups [20].

This study presented a dramatic case of variation in the prevalence of type 2 diabetes and obesity found in populations with similar genetic backgrounds living in different environmental conditions—traditional versus modern. These results indicate that, even in populations genetically prone to diabetes and obesity, their development is largely determined by environmental conditions. The results support the hypothesis that changes in lifestyle associated with modernization play a major role in the global epidemics of type 2 diabetes and obesity.

The data collected from this cross-sectional study comparing the Pimas of Arizona and Mexico and including the non-Pima Mexicans allowed for examination of other factors associated with obesity and type 2 diabetes. These factors included the role of energy expenditure in obesity, differences in the regulation of leptin, the contribution of insulin resistance and the prevalence of kidney disease.

Energy Expenditure

By comparing the physical activity level of 40 (17 female and 23 males) Mexican Pima Indians with 40 age- and sex-matched Pimas from the Gila River Indian Community (Arizona), the potential protective role of environment and physical activity against obesity was measured [21]. Total energy expenditure (TEE), measured with doubly-labeled

water, was used to assess physical activity as follows: 1) physical activity level (PAL) as the ratio of TEE on resting metabolic rate (RMR), 2) TEE adjusted for RMR by linear regression, 3) activity energy expenditure adjusted for body weight (AEE), and a translated questionnaire including occupational and leisure activity [22].

The PAL, TEE adjusted for RMR, and AEE adjusted for body weight results all showed that physical activity was higher in Mexican Pima when compared to Arizona Pima. The activity questionnaire indicated that Mexican Pima spend more time on occupational activities than Arizona Pima. Therefore we concluded that physical activity plays a significant role in the prevention of obesity in genetically susceptible populations [21].

Leptin

Leptin is an important signal for the regulation of energy stores. The impact of environment on leptin concentration was examined by comparing Mexican Pima Indians (N=224) still living a traditional lifestyle with Arizona Pimas (N=418) living a more modern lifestyle [23]. We hypothesized that the absolute value of leptin would be lower in Mexican Pimas because of their lower percent body fat, but that leptin could be further influenced by their lifestyle, independent of body composition. Indeed, leptin concentration was strongly correlated with percent fat in both groups. Among the Arizona Pimas, independent of percent fat, research participants with type 2 diabetes had lower leptin concentrations than non-diabetic participants. Among non-diabetic individuals, Mexican Pimas had lower absolute leptin concentrations than Arizona Pimas, but higher leptin concentrations after adjustment for percent body fat, waist circumference, age and sex. In a subset of seventy pairs of subjects matched for sex and percent body fat, leptin concentrations were significantly higher in Mexican Pimas than their Arizona counterparts. These results suggested that independent of body composition, leptin concentration may be increased by environmental factors, such as diet and physical activity [23].

Another aspect of the "thrifty gene" hypothesis was tested with the cooperation of the two Mexican populations in Maycoba (Pima and non-Pima) by examining leptin concentrations and resting metabolic rate [24]. Whereas the thrifty gene may be wreaking havoc with the health of the Pimas in Arizona it may continue to play a beneficial role in the Mexican Pimas. Due to their remote environment, with limited access to amenities associated with modernization, the Mexican Pimas remain lean and they potentially manifest physiologic mechanisms promoting the metabolic efficiency associated with the thrifty genotype. Because the non-Pima Mexicans living in the same village are of predominantly European heritage, and therefore not considered to possess the thrifty genotype, it is less likely they would express these metabolic characteristics. Therefore, we hypothesized that if low plasma leptin and low metabolic rate are expressions of the thrifty gene, this difference would be more apparent in the Pima versus non-Pima populations living in the same environment. To test this hypothesis non-diabetic Mexican Pima Indians (N=208) were compared with non-diabetic non-Pima Mexicans (N=183) living in the same environment. Leptin concentrations were strongly correlated with percentage body fat in both groups, yet there appeared no significant difference in plasma leptin concentrations between the groups. Similarly, no significant difference was shown in resting metabolic rate between groups. Therefore, these results did not support the hypothesis that hypoleptinemia, a low resting metabolic rate, or both hypoleptinemia and low resting metabolic, are expressions of the thrifty genotype.

Insulin Resistance

Insulin resistance has been identified as a major risk factor in the pathogenesis of type 2 diabetes and has been thoroughly studied in the Arizona Pimas [25]. Given the lifestyle differences between the Mexican Pimas and their genetically-related counterparts in Arizona, we hypothesized that the Mexican group would be less insulin resistant. The study population included 194 Mexican Pima Indians and 449 Arizona Pimas, all of whom had normal glucose tolerance. Results showed that Mexican Pimas are less insulin resistant than Arizona Pimas, even after adjusting for age, sex, and obesity [26]. These results emphasize the importance of lifestyle as a protective factor in the development of type 2 diabetes.

Kidney Disease

Another aspect of type 2 diabetes examination based on data obtained from Arizona and Mexican Pima Indians was the association between diabetes and kidney disease. The Arizona Pimas have an extraordinarily high rate of kidney disease attributable to diabetes and kidney failure is a leading cause of death. More than half of Arizona Pimas with type 2 diabetes develop clinical proteinuria within twenty years of diagnosis. Once proteinuria develops, an irreversible deterioration of kidney function often ensues that leads to end-stage renal failure [27].

Since both diabetes and kidney disease have genetic and environmental determinants, measures of urine albumin and creatinine concentrations were made from samples obtained in the Maycoba-wide survey of diabetes and obesity. Ultimately, the prevalence of elevated urinary albumin excretion proved higher in Pima Indians with diabetes than in those without, regardless of whether they lived in Arizona or Mexico. Therefore, although diabetes has major environmental

determinants, once diabetes develops, kidney disease will follow in populations susceptible to this complication [28].

Environmental Change

The original series of studies concluded that even in populations genetically prone to type 2 diabetes and obesity, their development is determined mostly by environmental circumstances. The environment is never static, however. Over the years, the environmental circumstances of the Mexican Pimas and non-Pimas have changed. A partial electrical supply became available and allowed access to television, cars were more readily available along with mechanized devices to alter energy expenditure, and small grocery stores dotted the main road.

In light of these changes, a 15-year follow up study began in 2010 to identify changes in the Maycoba environment and determine whether these changes were associated with differences in diabetes and obesity prevalence. Measurements made in the 1995 study were replicated as closely as possible, including a medical history, biochemical and anthropometric measures, physical activity and dietary assessments [17]. Early in the study, a repeat census was conducted to determine the current demographic profile of the study area. All women and men over 20 years old, regardless of ethnicity, were invited to participate. The population increased minimally between 1995 and 2010, and 94 % of the individuals who took part in the 1995 study participated in again 2010.

Some results were predictable while others were surprising. Over the 15-year timeframe, the age-sex-adjusted diabetes prevalence was unchanged in Mexican Pima men yet it increased in non-Pima men. Prevalence of type 2 diabetes tended to increase in both Mexican Pima women and non-Pima women. Body mass index increased in all groups [29]. Therefore, we concluded that the transition from a traditional to modernized lifestyle is associated with diabetes and obesity, regardless of genetic predisposition.

These results made it imperative to identify the details of modernization that preceded the increased prevalence of type 2 diabetes and obesity in Maycoba. Novel assessments were put into play to document environmental change. These included a qualitative assessment on gardening and cultivation perceptions and patterns, a land-use, land-cover analysis, and an examination of the food environment (acquisition, behavior, and availability).

The role of family gardens was examined with regard to their impact on food consumption and physical labor [30]. Qualitative methods—interviews, two focus groups, and a household survey–were employed to explore changes in gardening and cultivation practices over the fifteen-year span between the two studies. The main findings indicated that home gardens and large plots for cultivation continue to contribute significantly to the food supply, although the majority of Pimas believed that food from cultivation had declined along with the amount of work families and children put into gardening. This decrease was partially attributed to climate change (e.g., lower rainfall) and increased access to processed foods. These findings suggested that change has occurred, but not as dramatic as originally presumed. The physical activity linked to cultivation may continue as an important factor in weight control and thereby, the prevention of diabetes [30].

The ecological environment linked to potential changes in lifestyle was also examined through impacts to the landscape [31•]. A land-use and land-cover analysis was conducted of the Maycoba geographic area using aerial photos from 1994 and satellite images from 2007. This analysis was intended to examine transitions in the landscape, particularly from agricultural land-use to urbanized land-use, consistent with a decreased demand for physical activity. The findings indicated that the land-cover of the study area is mainly mixed vegetation and dense tree cover, a small percent of impermeable area, indicative of a rural environment. The land-use findings indicate a decrease or consistency in agricultural or ranching land and a decrease in farmland as seen through reforestation and re-vegetation in the Maycoba region. To examine lifestyle change three variables served as proxies: urban development, dwelling-unit density, and road network changes. The most notable changes were found in the town of Maycoba where urbanization, and the number and density of dwelling units increased. Only minor changes in the road network had occurred, as the interstate highway traversing the study area had opened prior to the start of the 1995 study. During the 15-year span the land-use and land-cover and proxy measures for lifestyle change in the Maycoba region have changed in a manner consistent with decreased physical activity [31•].

Changes in the food environment were also examined [32•]. Food acquisition was investigated through a representative household survey, two focus group discussions, and participant observation. The food retail environment changes were determined by auditing seven stores in the area. Findings showed that the food environment has changed dramatically in certain respects, with an increase in the presence of retail food stores, a wider selection of processed foods, an increase in perishable foods due the introduction of regular electricity, and the prominent placement of certain packaged foods. In juxtaposition, traditional subsistence-based activities such as cultivating, ranching, hunting, and gathering, remain important to daily life. Although there had been a noticeable decline in subsistence activities, a traditional lifestyle had persisted in the Maycoba region at the time of the follow-up study.

Conclusions

The Pimas of Arizona and Mexico have played a crucial role in scientific advances in type 2 diabetes and obesity. In

conjunction, the two groups have provided a unique opportunity to understand the independent roles of genes versus environment because they are genetically-related populations living in dramatically different environments yet presenting with significant differences in diabetes and obesity prevalence. These studies provided compelling evidence of the impact of environment and the protective role of a traditional lifestyle.

The impact of lifestyle change, from traditional to more modern, has been documented through investigations involving both Mexican Pimas and their non-Pima Mexican neighbors, populations not genetically related but who have experienced the same environmental changes over a 15-year span. These results highlight the potential downfall of this the type of environmental modernization.

Modernization is, however, inevitable and can bring many benefits to quality of life. When the food supply is enhanced and labor saving devices are invented it is incomprehensible that those who have not had access to such luxuries in the past will not embrace these advances. The challenge for the twenty-first century will be to identify and implement mechanisms for modernization throughout the developing world that take place in a manner that promotes health rather than impairs it and thereby protects the next generation from the inevitability of increased chronic disease.

Acknowledgments The 1995 research in Mexico was funded by National Institutes of Health grant DK-49947 to Leslie Schulz. The 2010 research in Mexico was funded by award number 5R01DK082568-02 from the National Institutes of Diabetes and Digestive and Kidney Diseases to Leslie Schulz. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Diabetes and Digestive and Kidney Diseases or the National Institutes of Health. We want to thank the participant communities for their invaluable contributions.

Compliance with Ethics Guidelines

Conflict of Interest Leslie O. Schulz and Lisa S. Chaudhari declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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