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EDITORIAL

Some common mistakes in the ethical considerations of research projects

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Clinical research, that is, research conducted with human beings, is a product of the 20th century. In the first half of that century, humanity learned that there must be an appropriate design, with a rigorous methodology, developing statistical tests and, later, qualitative methods. In the second half of the century, it was learned that it is not enough for a research protocol to be impeccable from a theoretical and methodological standpoint: it must also meet ethical requirements. In the second half of the century, it became clear that a research protocol must not only be flawless from a theoretical and methodological perspective but must also adhere to ethical standards.

Those who conduct research with human beings are usually very clear about the scientific quality of the research protocol. However, the regulatory aspect is often less known and, therefore, less understood. Hence, the most common mistake is probably confusing the ethical and legal regulatory systems. When this happens, which is quite frequently, legal documents are consulted to meet enforceable requirements, but not to act ethically. It ends up being more of an administrative act than an ethical one. In the Mexican context, it is common to consult the Regulations of the General Health Law on Health Research (RLGSMIS, particularly title two, and especially Articles 17, which addresses research risks, and Articles 20, 21, and 22, which address Informed Consent); since it is quite an old document, there are many aspects that are considered different from the ethical standpoint.

Unpublished data from the National Institute of Medical Sciences and Nutrition "Salvador Zubirán" show that the primary cause of rejection or non-approval by the Ethics in Research Committee is deficient informed consent letters. In published research conducted by Ethics Committees in second-level hospitals, informed consent letters may represent the second most common cause of rejection. Since the Nuremberg Code, emphasis has been placed on the issue of consent, both as a process and as the document that verifies this process has occurred; despite this, it remains a problem. Perhaps because a kind of universal form is often requested, merely to be filled out, without understanding its ethical relevance or the legal requirements.

Another example that can be cited, based on personal experience (there are no specific studies on this), is evaluating the risk involved in the interventions proposed in the research protocol. The RLGSMIS considers three types of research: no risk, minimal risk, and greater-than-minimal risk[1]. According to bioethics, it has been clear for decades that all research involves some type of risk, not necessarily biomedical. For example, administering a questionnaire, conducting an interview, or reviewing medical records carries risks, more of a psychosocial nature than a biomedical one, but it still involves risks. The Declaration of Helsinki has been clear on this matter since several revisions, including the most recent one[2]. In addition to this, it is not only about declaring the risks of the research but

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also about indicating how the identified risks will be minimized as much as possible. Furthermore, since all research carries risks, there must always be some form of benefits. To evaluate the risk, Article 17 of the regulation is usually referenced, but since it is neither fully read nor interpreted by legal experts (who could provide a more appropriate interpretation), the reference to Article 14 is often overlooked. In Section IV of Article 14, it states that the benefits must outweigh the risks. This is what is commonly understood in bioethical theory as the "risk/benefit balance." If this does not occur – that is, if the benefits (to the research subjects, the group they represent, science in general, and ultimately, the health of future individuals, in this order) are not greater than the risks – the research should not be authorized by the Ethics in Research Committee.

In Mexico, there is a guide developed by the National Bioethics Commission (CONBIOETICA) for the integration and functioning of Ethics in Research Committees[3]. All stakeholders in research should read it, not only those who are part of the Ethics Committees, but also those who conduct research. In this way, they would understand what is being requested of them. The guide clarifies that the protocol must satisfy both legal and ethical requirements. It mentions both, using a conjunction, not a disjunction, which clearly defines that these are two realms that, while related, have their own specificities.

Based on these paragraphs, it is possible to propose that the most common mistake when making the ethical considerations of a research protocol is focusing on legal requirements, rather than the truly ethical ones. It is only when it is understood that the theoretical approaches and methodological aspects of a research project carry an ethical dimension that the importance of the ethical dimension and its proper evaluation by Ethics in Research Committees will be recognized.

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ORIGINAL ARTICLE

Vitiligo and thyroid disease: frequency in patients from a tertiary care hospital dermatology service from 2021 to 2023

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Abstract

Background: *Vitiligo is an autoimmune condition causing skin depigmentation due to melanocyte loss. Patients with vitiligo are at higher risk for thyroid diseases. Because of this, the study was made to see the frequency at Hospital Juárez in Mexico.* **Objective***: The objective isto determine the frequency of thyroid disease in patients with vitiligo at the Juárez Hospital of Mexico during 2021, 2022, and 2023.* **Methods***: This observational, cross-sectional, retrospective study evaluated vitiligo patients at Hospital Juárez de México from 2021 to 2023. Data were collected from dermatology consultation sheets to identify vitiligo cases, and medical records were reviewed for thyroid disease.* **Results***: A total of 95 patients with vitiligo were identified, 25 (26.4%) of whom were also diagnosed with thyroid disease. The most common thyroid condition was hypothyroidism (23.2%). The average age of these patients was 49.2 years, with 92% being female. TSH (Thyroid Stimulating Hormone) levels showed the highest significance ($p < 0.001$), and diabetes was the most common comorbidity (14.7%).* **Conclusion***: In our sample, we observed a vitiligo prevalence of 26.4%, which is consistent with previous findings in the literature. This result suggests that patients at Hospital Juárez de México may have a prevalence of thyroid disorders comparable to that reported in other studies conducted in the country.*

Keywords: *Vitiligo. Frequency. Autoimmune. Thyroid disease.*

Introduction

Vitiligo is a skin depigmentation disorder with a global prevalence of 0.5-2% and is more common in India (8.8%) and Mexico (2.6-4%)[1]. Prevalence increases with age, especially in people over 60, while incidence is higher in individuals under 20[2]. In Mexico, vitiligo ranks third in dermatological consultations. It affects not only the health aspect of those who suffer from it but also their social and psychological well-being due to the characterized white spots, which can be small or large and typically affect the hands, feet, face, knees, elbows, and scalp and can lead to stress, anxiety, depression, and low self-esteem[3].

Vitiligo has an autoimmune origin, where genetic and environmental factors attack melanocytes. Autosomal dominant inheritance and genetic predisposition have been identified, involving several genes related to both innate and adaptive immunity. Oxidative stress also plays an important role in the destruction of melanocytes. It is often not isolated but associated with other diseases, mostly autoimmune, metabolic, and dermatological. Understanding these associations is important for providing comprehensive patient care, which is done at Hospital Juárez de México, where consultations continue to increase yearly[4,5].

To understand the association with comorbidities that impact the quality of life, thyroid disease should be highlighted, as it has been recognized as an illness mediated by T-cells, which is related to the expression of the HLA-DR allele. In addion, vitiligo patients have

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a higher proportion of positive antithyroid antibodies, suggesting a marked association between these diseases. In Mexico, the frequency has been reported to range from 21.5% to 26.4%. This study aims to determine how frequent this association is at the hospital to begin a comparative analysis, which could be useful in examining the frequency of vitiligo cases and establishing thyroid disease as a potential risk factor, further supporting the association between both conditions[4,5].

The clinical practice guidelines for vitiligo only mention that there is a relationship with autoimmune diseases without elaborating on which ones are the most common or their prevalence. Given the prevalence, more emphasis should be placed on identifying these autoimmune diseases, how they present with vitiligo, and recognizing thyroid disease as a particularly important factor. Not only because of its association with vitiligo but also because thyroid disease is a condition with high incidence in the population and plays a crucial role in the body's functioning, impacting multiple systems. Therefore, understanding its frequency is essential for early detection in vitiligo patients who may have a predisposition to thyroid disease, allowing for more targeted treatment for both conditions[6].

Based on the previous frequency reports, the hypothesis for the study is that the main thyroid diseases would be the same as those reported in the literature, and the frequency we expect to find will be approximately 20% of the cases. This is to determine the frequency of thyroid disease in patients with vitiligo at Hospital Juárez de México during the years 2021, 2022, and 2023, characterizing patients by age, gender, socioeconomic status, marital status, occupation, and comorbidities to identify the most common risk factors in patients with vitiligo at Hospital Juárez de México and finally determine the most frequent thyroid diseases in these patients[7].

Materials and methods

Study design

This study was designed following the preferred reporting items for cross-sectional studies of the STROBE Statement. This is an observational, cross-sectional, retrospective with a selected population of all patients diagnosed with vitiligo at Hospital Juárez de México in the years 2021, 2022, and 2023 by collecting data from patients initially using daily consultation sheets from the Dermatology service to identify patients with vitiligo in the years mentioned. Subsequently, using physical and digital medical notes, as well as thyroid markers, were used to identify thyroid disease in each patient.

Inclusion and exclusion criteria

The inclusion criteria encompassed all patients who attended consultations at Hospital Juárez de México, were diagnosed with vitiligo, and had a thyroid profile available from 2021 to 2023.

Variables

The selected variables for the study were: the presence of thyroid disease, referring to whether the patient had any disorder related to the thyroid, TSH, T3, and T4 laboratory levels, age, gender, occupation, marital status, and the existence of any comorbidity associated, including diabetes mellitus, asthma, anemia, alopecia, obesity, and lupus.

Statistical methods

The statistical analysis was performed using IBM Statistical Package for Social Sciences software. We collected all the data to analyze frequencies and percentages (valid and cumulative), measures of central tendency (mean and median), Chi-square tests, and, finally, to create graphs.

Results

A total of 125 patients were registered; of those, 95 patients diagnosed with vitiligo and thyroid markers were identified with a complete medical history, and of the 95, 25 were already diagnosed with thyroid disease, resulting in a frequency of 26.4%. Among the thyroid diseases, the most frequent was hypothyroidism at 23.2%, followed by hyperthyroidism at 2.1%, and one case of papillary cancer, representing 1.1%. An average age of 49 years was found in this group, with the majority being female (92%). In terms of marital status, 64.2% were single, 25.3% married, 7.4% in a free union, and 3.2% widowed. The occupation: homemakers (64%) were the most common, followed by merchants (16%).

An analysis of laboratory tests was conducted on 69 patients, all of whom had complete tests. Levels in all cases using the Chi-square test showed a statistically significant result ($p = 0.002$). The average T3 level among 69 patients was 1.12, within the normal range of 0.79-1.49. Most patients (68.1%) had normal T3

Table 1. Relation between T3 and thyroid disease diagnosis

Categorized T3	No (n = 44) (%)	Hyperthyroidism (n = 2) (%)	Hypothyroidism (n = 22) (%)	Papillary cancer (n = 1) (%)
Normal	34 (77.3)	0 (0)	12 (54.5)	1 (100)
High	7 (15.9)	2 (100)	2 (9.1)	0 (0)
Low	3 (6.8)	0 (0)	8 (36.4)	0 (0)

Table 2. Relation of TSH in the diagnosis of thyroid disease

Categorized TSH	No (n = 44) (%)	Hyperthyroidism (n = 2) (%)	Hypothyroidism (n = 22) (%)	Papillary cancer (n = 1) (%)
Normal	41 (93.2)	1 (50)	11 (50)	0 (0)
High	3 (6.8)	0 (0)	8 (36.4)	0 (0)
Low	0 (0)	1 (50)	3 (13.6)	1 (100)

levels, with 49% having no thyroid disease, 17% with hypothyroidism, and 1.44% with papillary cancer. Elevated T3 levels were found in 15.9% of patients, with 10.11% having no thyroid disease and 2.89% split between hypothyroidism and hyperthyroidism. Similarly, 15.9% had low T3 levels, with 4.33% having no thyroid disease and 11.56% having hypothyroidism (Table 1).

The average free T4 level was 1.19, within the normal range of 0.71-1.85. Most results were normal, with 89.9% of patients showing normal free T4 levels. Of these, 62.35% had no thyroid disease, 26.1% had hypothyroidism, and 1.45% had hyperthyroidism. Elevated free T4 levels were found in 5.8% of patients, each with different diagnoses: without thyroid disease, hyperthyroidism, hypothyroidism, and papillary cancer. Low free T4 levels were observed in 4.3% of patients, all of whom had hypothyroidism. In the same way, we found a good statistical significance in the Chi-square tests (p = 0.009).

The average total T4 level was 8.66, with a normal range of 4.50-12. Total T4 levels were normal in 82.6% of patients, with 59.41% not diagnosed with thyroid disease, 20.28% having hypothyroidism, and 1.44% having hyperthyroidism or papillary cancer. Elevated total T4 was found in 13% of patients, most of whom had hypothyroidism. Low total T4 levels were found in 4.3% of patients, with 2 having no thyroid disease and 1 with hypothyroidism (Fig. 1).

The TSH level gives an average of 4.32 with a normal range of 0.49-4.67, with the highest significance among the laboratory tests (< 0.001) in the Chi-square test. We found that of the 53 patients (76.8%) with normal TSH, 41 (59.41%) are patients without a thyroid disease diagnosis, 11 (15.9%) have hypothyroidism, and 1 (1.44%) has hyperthyroidism.

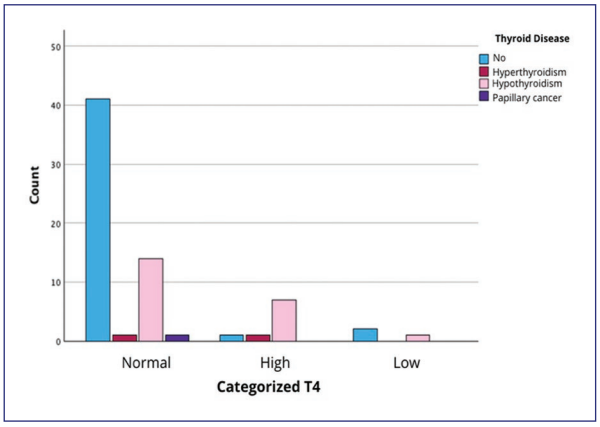

Figure 1. Relation between total T4 and thyroid disease diagnosis.

Elevated TSH was found in 11 patients (15.9%), of which 3 (4.3%) have no thyroid disease diagnosis and 8 (11.56%) have hypothyroidism. Finally, for low TSH, we have five patients (7.2%), of whom 3 (4.32%) have a diagnosis of hypothyroidism and 1 (1.44%) have hyperthyroidism (Table 2).

In addition to thyroid disease, related conditions identified in the vitiligo patients included diabetes (14.7%), asthma (4.2%), alopecia (3.2%), anemia, and lupus (1.1% each). In addition, 53.7% of patients were overweight or obese (Table 3).

Discussion

According to the literature in Mexico, Salinas-Santander et al. (2014) and Escobar-González et al. (2017) reported prevalences of 22.2% and 26.4%,

Table 3. Patients with a diagnosis of diseases related to vitiligo

Condition	Yes (n = 74) (%)	No (n = 496) (%)
Diabetes	14 (14.7)	81 (85.3)
Asthma	4 (4.2)	91 (95.8)
Alopecia	3 (3.2)	92 (96.8)
Anemia	1 (1.1)	94 (98.9)
Lupus	1 (1.1)	94 (98.9)
Obesity/Overweight	51 (53.7)	44 (46.3

respectively, matching the frequency observed in our sample. Our findings support this consistency, with a vitiligo prevalence of 26.4%. This suggests that patients at Hospital Juárez de México may have a prevalence of thyroid disorders comparable to that documented in other studies conducted in the country.

The average age of all patients in the study was 39.56, while those with both vitiligo and thyroid disease were 49.20. Most patients were women (77.9%), and a higher prevalence of both conditions was observed in females (92%) compared to males (8%). This aligns with previous literature that reports a higher incidence in women (0.5-1.3%) versus men (0.2-1.1%).

Stress was considered a potential trigger for lesion development; therefore, occupation and marital status were analyzed as variables. Most patients were single and worked as homemakers, suggesting that both factors may contribute to increased stress levels, potentially influencing the onset or progression of the disease.

Laboratory tests for thyroid disease (T3, T4, TSH) were performed. TSH is the best marker for thyroid function and is expected to be low in hyperthyroidism and high in hypothyroidism. T4 is high in hyperthyroidism and low in hypothyroidism, while T3 is elevated in hyperthyroidism and less helpful in diagnosing hypothyroidism. In the Hospital Juárez de México, 22 patients had hypothyroidism, 2 had hyperthyroidism, and 1 had papillary cancer. For hypothyroid patients, eight had elevated TSH levels, but some had unexpected results, including elevated T4 levels, which contrasts with typical expectations. For hyperthyroid patients, the results were consistent with the literature, showing low TSH, elevated T4, and T3.

Common comorbidities with vitiligo were observed, with diabetes being the most frequent (14.7%), followed by asthma, alopecia, anemia, and lupus. The strong association between diabetes and vitiligo, particularly type 1 diabetes due to shared immune-mediated destruction, supports the significance of diabetes as the most common disease in our study.

Conclusion

In our sample, we observed a vitiligo prevalence of 26.4%, which is consistent with previous findings in the literature. This result suggests that patients at Hospital Juárez de México may have a prevalence of thyroid disorders comparable to that reported in other studies conducted in the country.

Funding

The authors declare that this work was carried out with the authors' own resources.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The authors have obtained approval from the Ethics Committee for the analysis of routinely obtained and anonymized clinical data, so informed consent was not necessary. Relevant guidelines were followed.

Declaration on the use of artificial intelligence. The authors declare that artificial intelligence was used in the writing of this manuscript [specify the tool and all sections of the manuscript where it was used].

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RESEARCH LETTERS

A complete type 2 diabetes remission by following a Mexican traditional diet. A case report

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Abstract

Type 2 diabetes (T2D) complete remission is defined as normoglycemia for at least 1 year, in the absence of active pharmacologic or surgical therapy. This report describes a complete remission case, which was achieved through a Mexican traditional diet and last for 4 years. Mexican traditional diet shares with the Mediterranean diet a pattern of high consumption of fresh fruits and vegetables, whole grains, and higher-fat dairy foods, with a protective effect against chronic inflammation and insulin resistance. Adequate control and even complete remission of T2D is possible through an affordable diet available to most of the Mexican population.

Keywords: *Diet. Insulin resistance. Type 2 diabetes. Complete diabetes remission. Lifestyle changes.*

Introduction

Type 2 diabetes (T2D) has been considered as a chronic progressive disease that can be controlled but not cured[1]. The American Diabetes Association announced a consensus statement defining diabetes complete remission as normoglycemia for at least 1 year, in the absence of active pharmacologic or surgical therapy[2,3]. T2D remission can be accomplished by bariatric surgery or lifestyle changes such as weight loss and exercise[4,5]. Low-carbohydrate, ketogenic, vegetarian, vegan, low-glycemic index, high-fiber, low-fat, high-protein, and Mediterranean diets are among the dietary interventions used to treat T2D[6,7]. The Mexican diet is considered a culprit in the ever-increasing rates of obesity and diabetes in Mexico. However, here we present a well-documented case of complete T2D remission achieved through a lifestyle change based on a traditional Mexican diet.

Case report

An asymptomatic, normotensive (120/80 mmHg), overweight (waist circumference 100 cm, body mass index (BMI) 26 kg/m^2), sedentary, 49-years-old man with a family history of diabetes was diagnosed with T2D, based on fasting blood glucose and glycosylated hemoglobin values, after a blood donation. Laboratory findings revealed venous blood glucose of 312 mg/dL (17.32 mmoL/L), A_{1C} of 8.0%, total cholesterol of 202 mg/dL, high-density lipoprotein (HDL) cholesterol of 36 mg/L, and triglycerides of 427 mg/dL (4.87 mmoL/L). Hyperglycemia, hypertriglyceridemia, and low HDL values were the criteria for metabolic syndrome. According to a 24-h diet reminder questionnaire, the patient had an everyday consumption of 12 558 kJ (3,000 kcaL), with an adequate intake of dietetic fiber (35.2 g) and proteins (20%), but with a low consumption of carbohydrate (41%) and a high ingestion of fat (39%). Treatment consisted of lifestyle changes, especially the observance of specific menus based in a traditional Mexican diet aimed to provide a gradual reduction to 8,372 kJ (2,000 kcaL), 55-60% carbohydrates, 25% of fat and 20% of proteins. This diet is mainly based on beans, corn tortillas, fruits, vegetables–including cactus (nopales, *Opuntia ficus-indica*) and roots (jicama, *Pachyrhizus erosus*)–, rice and distinct kinds of meats.

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Weight was registered, and the subject receives personal diet counseling. Dietary compliance was monitored by a 24-h diet reminder questionnaire. In addition, the subject was advised to walk 30 min/day, 5 days a week. Five weeks later, the patient showed BMI < 25 kg/m^2, capillary pre-prandial glucose < 100 mg/dL (5.5 mmoL/L), and post-prandial < 120 mg/dL (6.6 mmoL/L). Six months later, the patient's renal filtration rate was 94 mL/min, and an oral glucose tolerance curve was performed. In this test, basal glucose was 97 mg/dL (5.38 mmoL/L), and the glucose values at 30,' 60,' 90' and 120' were 190, 171, 129, and 89 mg/dL (10.5, 9.5, 7.2 and 4.9 mmoL/L), respectively. After 10 months, A_{1C} was as low as 5.3% and remains under normal values after more than 3 years, as can be seen in Fig. 1. After 40 months, the patient presents a 23.3 kg/m^2 BMI, glucose of 96 mg/dL (5.3 mmoL/L), A_{1C} of 5.3%, insulin of 5.96 μU/mL (41.3 pmoL/L), homeostatic model assessment-insulin resistance (HOMA-IR) of 1.41, and triglycerides of 115 mg/dL (1.31 mmoL/L).

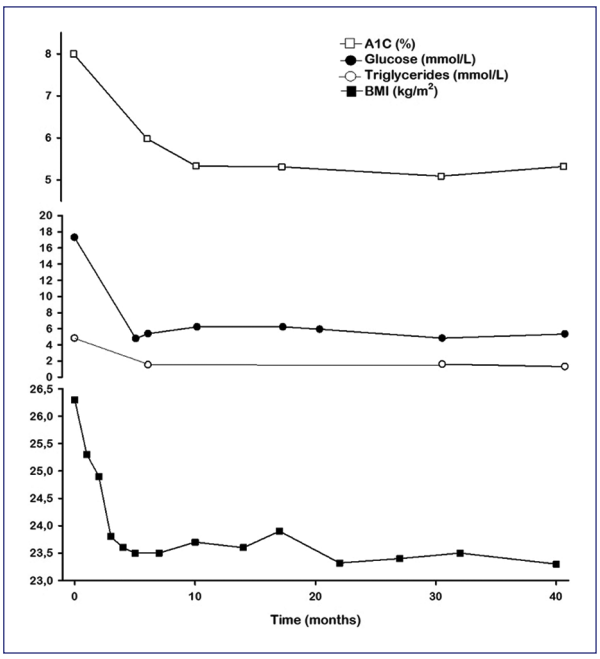

Figure 1. Time course of type 2 diabetes predictors in a Mexican subject following a Mexican traditional diet. A set of T2D predictors; body mass index (kg/m^2), glucose (mmoL/L), A_{1C} (%) and triglycerides (mmoL/L) were measured at the indicated times before (time = 0) and after starting the intervention.

Discussion

This report describes a complete remission case that was achieved through a Mexican traditional diet and moderate exercise[8]. Large, controlled trials showed that an intensive lifestyle intervention on subjects with T2D increases the prevalence of complete remission from 2 to 11.5% in 1 year[9-11]. However, a complete remission in community settings is very rare (0.24 cases/1,000 person-years), Karter et al. report it is mainly observed in African American subjects older than 65 years, with < 2 years since diagnosis, a primary A_{1C} < 5.7%, and no diabetes medication at baseline[12,13].

Dietary balance is a relevant lifestyle intervention for T2D treatment. Among the different dietary interventions that have been used to treat T2D, such as low carbohydrate and ketogenic diets which have shown weight loss and good glycemic control, but increased mortality rate[14], Mediterranean diet has so far shown the greatest improvement in glycemic control and a clear tendency to favor T2D remission[15]. A Mediterranean diet containing a high proportion of monounsaturated fat has a protective effect against chronic inflammation and IR[16]. Mexican traditional diet shares with the Mediterranean diet a pattern of high consumption of fresh fruits and vegetables, whole grains, and higher-fat dairy foods. Interestingly, an increase in insulin sensitivity upon consumption of a traditional Mexican diet has been described[17]. In addition, Traditional Mexican Cuisine was inscribed as an Intangible Cultural Heritage of Humanity in 2010. In this case, we describe a Mexican diabetic subject, younger than 65 years old, with a primary A_{1C} > 5.7% and no medication at baseline that after following a Mexican traditional diet reaches normal glucose values in a remarkably short time and even shows an improvement in insulin sensitivity, reflected by a HOMA value of 1.41. To the best of our knowledge, this is the first case describing a T2D complete remission lasting more than 3 years achieved through Mexican traditional diet and exercise in a Mexican subject[18].

Due to the alarming increase in obesity and T2D prevalence, an epidemiological emergency was declared in Mexico. Among other factors, the Amerindian genetic background of the Mexican population that predisposes to T2D, the massive consumption of soda beverages, and a sedentary lifestyle most likely are the major contributors to this troubling trend[19]. In this context, T2D has reached an alarming 18.2% prevalence[20], and it has been estimated that only a quarter of the affected people are really following the blood glucose control recommendations[21]. To achieve a proper T2D management among the Mexican population through the Mediterranean diet is challenging because adherence to it implies profound changes in alimentary

behavior that, in addition, are expensive for the average Mexican. The relevance of our findings is that an adequate control and even complete remission of T2D is possible through an affordable diet available to most of the Mexican population.

Conclusion

This report presents a case showing that adequate control and even complete remission of type 2 diabetes can be achieved through the adoption of a traditional Mexican diet.

Funding

The authors declare that this work was carried out with the authors' own resources.

Conflicts of interest

The authors declare that they have no conflicts of interest. A.J.R.M. and A.M. took active care in the reported patient's clinical course. A.M. and S.A. researched data and wrote the manuscript. A.M. is the guarantor of this work and, as such, has full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors reviewed and commented on subsequent drafts of the manuscript.

Ethical considerations

Protection of humans and animals. The authors declare that the procedures followed complied with the ethical standards of the responsible human experimentation committee and adhered to the World Medical Association and the Declaration of Helsinki. The procedures were approved by the institutional Ethics Committee.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from patients, and received approval from the Ethics Committee. The SAGER guidelines were followed according to the nature of the study.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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BRIEF COMMUNICATION

Extracorporeal photopheresis reduces clinical signs of chronic graft versus host disease in pediatric patients: a case series report

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Abstract

Background: *Graft versus Host Disease (GVHD) is a frequent pathology that affects around 60% of patients who receive allogeneic hemopoietic stem cell transplantation. The first-line treatment is corticosteroids. However, some of the patients are or become resistant to this therapy. Extracorporeal photopheresis (ECP) represents an alternative for such limitation, with no antecedents to induce resistance. The mechanisms involved in its effect are still unknown, and most of the studies developed in adults or in vitro. In the case of pediatric patients, there is few information in the literature.* **Clinic Case:** *Four pediatric patients previously diagnosed with chronic GVHD and identified as corticosteroids resistant. There were three evaluations of GVHD severity by organs and overall score before and after ECP sessions as indicates for each case. We identified T cell subpopulations using antibodies and analyzed them by flow cytometry from peripheral blood samples. There was a decrease in the severity of GVHD from the sixth session, and no preference for target tissue was observed. There was no difference between T cell subpopulations analyzed before and after ECP.* **Conclusion:** *ECP is an efficient therapy to treat chronic GVHD in pediatric patients.*

Keywords: *Extracorporeal photopheresis. T cells. Graft versus host disease. Chronic. Case series report.*

Introduction

Human leukocyte antigen (HLA) compatibility is the primary criterion for receiving a transplant. In the clinical area, the most polymorphic alleles are analyzed, including HLA-A, -B, -C, -DP, -DQ, and -DR. The graft for hematopoietic stem cell transplantation consists in progenitor cells (CD34+) along with mature CD4 and CD8 T cells. Some hemopoietic stem cell transplantation (HSCT) protocols include T cell -depletion from the graft before transplantation. Some T cells in the graft might recognize donor HLA-derived peptides. Consequently, donor-specific T cells will activate and produce cytokines: Interferon-gamma (IFN-γ), tumor necrosis factor-alpha (TNF-α) and acquire cytotoxic activity. The constant presence of the alloantigen (as all recipient cells express it) will maintain T cell expansion. Consequently, memory T cell generation will occur, including central: Tcm and effector: Tem subpopulations. Tem cells can respond faster and express higher levels of cytokines, such as IFN-γ and TNF-α[1]. Alloreactive cells have tissue targets such as the skin,

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mucosal tissues, gastrointestinal (GI) tract, and liver, which represent the main clinical signs during: Graft versus host disease (GVHD). Its prevalence ranges from 30% to 70 % of all HSCT cases[2].

GVHD is classified according to the time post-HSCT when it is diagnosed, as either acute (within the first 100 days) or chronic (after the first 3 months). In the first one, CD4 and CD8 T cells are associated to the damage. Meanwhile, B cells and T cells are for chronic GVHD[3].

The first line of treatment is corticosteroids. However, approximately 50% of patients are or become refractory[2]. In those cases, other treatments should be considered.

Extracorporeal photopheresis (ECP) was approved by Food and Drugs Administration to treat T-cell cutaneous lymphoma[4] in the 80's. This therapy involves exposing approximately 10% of peripheral blood volume[5] to a deoxyribonucleic acid-intercalating agent, 8-methoxypsoralen (8-MOP)[6]. That means that all those cells proliferating (as activated T cells) will be the target of ECP, inducing their death. Cells exposed will die by apoptosis, just a few hours after 8-MOP. Eliminating alloreactive cells will likely reduce clinical GVHD score and, in turn, corticosteroid dose reduction.

Most of ECP knowledge comes from observations in adult patients[7-10], in whom, a clear efficacy and low adverse effects have been reported.

New evidence observed in children patients will increase the knowledge of ECP in these populations[11-14]. As well as the effect on T subpopulations and clinical symptoms reduction.

This work presents a case series report. All four cases received hematopoietic stem cell transplantation after granulocyte-colony stimulator factor-mediated mobilization. GVHD was diagnosed according to the criteria established by Jagasia et al.[15] for the pediatric population[16], categorized as mild, moderate, and severe grades. For all of them, the first line of treatment was corticosteroids and then, added an off-line ECP using CELLEX Therakos™ Systems. ECP sessions were every other day. No patient suffered any adverse effects associated to the therapy.

Case 1

A 3-years-old male was diagnosed with acute myeloid leukemia (AML). HLA-matched was 50% for analyzed alleles. Clinical score included cutaneous, ocular, pulmonary, GI tract, and skeletal muscle signs. He received twelve sessions, and GVHD was evaluated before, 24 h after the sixth and twelfth sessions. After six sessions, all signs except cutaneous, decreased the severity. However, none disappeared after the twelve sessions (Fig. 1). Analysis of T cell populations revealed no difference before and after therapy (Table 1).

Case 2

A 5-year-old male with an AML diagnosis. HLA-matched was 50%. He received twelve sessions, and clinical evaluations were conducted at the beginning, 24-h after the sixth and twelfth sessions. Initially, there were cutaneous, ocular, pulmonary, GI tract, genital and skeletal muscles signs. After six sessions, GI tract signs reduced, but they were still present at the twelfth session. Cutaneous, ocular, and pulmonary injuries decreased the severity, while skeletal muscle and genital signs disappeared (Fig. 1). T cell subpopulation analysis showed no difference before and after the treatment (Table 1).

Case 3

A 4-year-old female with an acute lymphoid leukemia (ALL) diagnosis. Moreover, a 100% HLA-matched. She received twelve sessions and a clinical evaluation at the beginning and 24 h after the sixth and twelfth sessions. At the beginning of the therapy, there were pulmonary, GI tract, and liver injuries. In the sixth session, pulmonary severity was maintained, but GI tract and hepatic severity were decreased (Fig. 1). Analysis of T cell subpopulations did not show a difference between the beginning and the end por ECP (Table 1).

Case 4

A 13-year-old female with an ALL diagnosis. And a 75% HLA compatibility. Initially, there were cutaneous signs. Twenty-four hours after receiving three sessions, no changes were observed (Fig. 1). Analysis of T cell subpopulations revealed no difference before and after treatment (Table 1).

Discussion

Here, we detected the first changes since the sixth session. Treatment with psoralen 8-MOP and ultraviolet A light, applied to a fraction of blood cells, is sufficient to induce immunomodulatory effects. Previous studies described that monocytes phagocytosed apoptotic

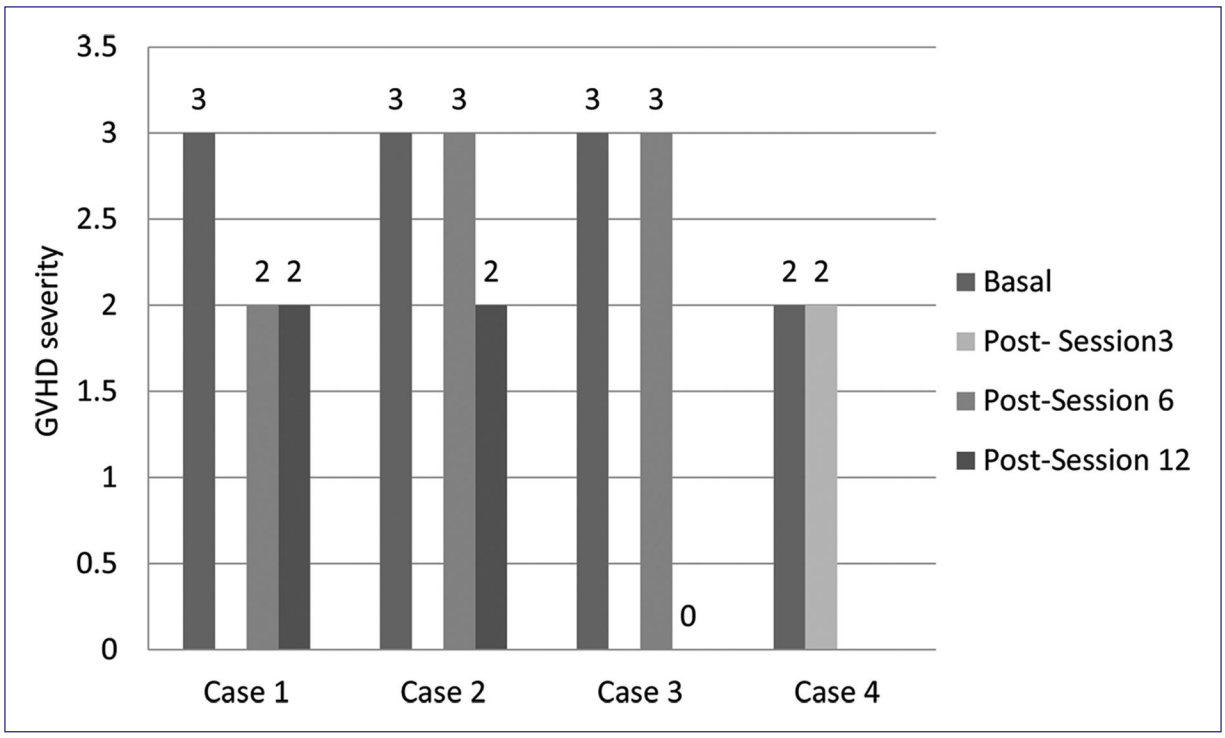

Figure 1. Global response of graft versus host disease patients during extracorporeal photopheresis treatment. Clinical evaluation was done after three sessions (case 4) or twelve sessions (cases 1, 2, and 3).

Table 1. Frequency of T cells subpopulations pre-and post-ECP

T cell subpopulation	Pre-ECP absolute number/uL Mean (95% CI)	Post-ECP absolute number/uL Mean (95% CI)	p
CD4			
Naïve: CD3 + CD4 + CD45RA + CD62L + CCR7 +	20.62 (–13.27, 54.52)	10.7 (–6.84, 28.24)	0.465
Effectors: CD3 + CD4 + CD45RA + CCR7–CD62L–	3.57 (–5.89, 113.04)	17.8 (–1.80, 37.40)	0.068
Central memory: CD3 + CD4 + CD45RO + CD62L + CCR7 +	23.05 (–38.48, 84.58)	10.15 (4.52, 15.77)	0.715
Effector memory: CD3 + CD4 + CD45RO + CD62L + CCR7–	43.82 (–40.02, 127.67)	31.9 (–20.57, 84.37)	0.465
CD8			
Naïve: CD3 + CD4 + CD45RA + CD62L + CCR7 +	10.45 (–6.42,27.32)	18.97 (–36.21, 74.16)	0.715
Effectors: CD3 + CD4 + CD45RA + CCR7-CD62L–	13.65 (–1.74, 29.04)	3.82 (–0.19, 7.84)	0.109
Central memory: CD3 + CD4 + CD45RO + CD62L + CCR7 +	1.72 (–0.16, 3.6)	0.77 (–0.28, 1.83)	0.068
Effector memory: CD3 + CD4 + CD45RO + CD62L + CCR7–	92.5 (–18.19, 203.19)	70.87 (7.47, 134.27)	0.465

Peripheral blood samples of all participants were recolected by the time of the first session (Pre-ECP) and after (24 h) after the past session (Post-ECP). Then, the phenotyping of different indicated cells was analyzed by flow cytometry. Statics analysis was performed using the Wilcoxon rank test. ECP: extracorporeal photopheresis; CI: confidence interval.

bodies of proliferating cells (mainly alloreactive T cells) after psoralen and ultraviolet A light exposure. This contributes to the induction of tolerogenic Dendritic cells[17] and a reduction in the expression of co-stimulatory molecules on their surface[18]. In the case of T cells, there is an increase of regulatory T cells (Treg), specifically those expressing Foxp3+[19]. These cells will mediate the inhibition of proliferation, differentiation, and effector functions of alloreactive T cells[20]. In the case of GVHD, naïve T cells are considered important players in the high-severity disease compared to those mediated by Tcm or Tem cells[21-24]. The primary difference lies in the frequency of T cells recognizing minor antigens which may activate and elicit a response against the recipient[25]. The most studied is the H-Y antigen, also known as the male antigen[26]. In mouse

models, mediated GVHD pathology. Other examples of these antigens are CD45[27] and H60[28]. In our analysis of T cell subpopulations, no significant differences were observed in the efficacy of ECP, consistent with other publications[19,29,30]. We observed a trend for effector T cells to decrease in frequency. However, one limitation of the present work is the small number of patients included and the time points of monitoring T cells in peripheral blood. We considered that at longer time (at least 3 months after treatment) may reveal differences between CD4 and CD8 T cells, as reported in previous reports[19,29-32]. However, we consider that the clinical impact observed should be associated with a decrease in effector T cells that migrate to target organs (such as the lungs, skin, GI tract, and liver) as these are associated with GVHD[33-38].

Moreover, there is no hierarchy of clinical improvement depending on the tissue. This means that ECP may be used for any GVHD organ target. The use of immunosuppressors will impact the immune response against pathogens, and hematopoiesis reconstitution. In that way, those alternatives that target activated T cells to treat GVHD are useful. Our work provides more evidence of the effectiveness of ECP in safely treating chronic GVHD for pediatric patients.

Conclusion

ECP is an efficient therapy to treat chronic GVHD in pediatric patients.

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The authors declare that this work was carried out with the authors' own resources.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The authors have obtained approval from the Ethics Committee for the analysis of routinely obtained and anonymized clinical data, so informed consent was not necessary. Relevant guidelines were followed.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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