Twenty-five years of knowledge of the prevention of neural tube defects with folic acid

Antibiotic self-medication in university students from Trujillo, Peru

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<td>Hematology and Internal Medicine Center, Ruiz Clinic of Puebla, Puebla, Mexico</td>
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<td>Hematology Service at the “Santa Creu i Sant Pau” Hospital, Barcelona, Spain</td>
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Twenty-five years of knowledge of the prevention of neural tube defects with folic acid

Folic acid (FA) is a vitamin that belongs to the group B complex (B9). Its main sources are green leafy vegetables and legumes and citrus fruits, among others. Its deficiency is associated with anemia. However, what has come to catapult FA as a vitamin important to health, is the discovery that women with deficient FA blood levels have an increased risk of a defective childbirth due to the abnormal development of the nervous system, particularly anencephaly and spina bifida, known as neural tube defects (NTD). Periconceptional FA consumption decreases the risk of having a child with these malformations by up to 70%.

The first studies regarding this benefit in pregnancy were performed by Smithiels et al. in 1980, who found that women who had a child with these defects had lower levels of formiminoglutamic acid excretion (FIGLU), a test that identifies a deficiency of folic acid and vitamin B12, compared to those whose children were born healthy.³ On the other hand, mothers with a history of childbirth with NTDs are at greater risk of having another child with the same defect. This led researchers to analyze the probability of reducing the recurrence of NTDs by supplementation with FA before pregnancy, where they achieved a significant reduction in cases by consuming 4 mg of folic acid a day.⁴ After the results were obtained, they are given the task of investigating if supplementation could also reduce the incidence of NTDs, which was demonstrated and published in 1991.⁵

The next step was to find ways to raise the levels of folic acid in women of childbearing age, especially before pregnancy occurs. Strategies have been diverse, from promoting a diet of foods high in folate (the form of the vitamin in foods) to FA supplement tablets, at doses that vary according to the rules in different countries (0.4–0.8, micrograms/day or 5 mg/week). Another strategy is to use food fortified with FA, which ensures better bioavailability of the compound compared with that of natural origin.

Although there has been irrefutable evidence that folic acid prevents childbirth with neural tube defects (anencephaly, spina bifida) for 25 years, it has not been possible to position the knowledge in the medical community or among women of childbearing age. While it is true that health professionals recommend the consumption of folic acid in women during pregnancy for the prevention of neural tube defects, consumption is necessary for three months before pregnancy because the embryonic nervous system develops between the third and fifth weeks, even before the woman realizes she is pregnant. In addition to that, about 40% of pregnancies are unplanned, and strategies to increase consumption of the vitamin B complex have failed in most countries.

Folic acid intake, either through supplementation or by eating fortified foods, should be a policy similar to the application of vaccines due to the prevention level obtained from these equally disabling and mortal diseases. Thanks to that vaccination campaigns which have achieved the virtual eradication of polio, NTDs are currently the most important cause of motor disability.

The United States of America have carried out food fortification with folic acid to help raise blood levels. However, it has been seen that further supplementation by consumption of a tablet containing 0.4 mg daily is necessary. They have fortified wheat, flour and corn in our country. Never the less, this is not enough to achieve blood levels sufficient for protection, requiring additional supplementation.

Consuming foods rich in folate (green vegetables, citrus fruits, liver, etc.) helps, but is not enough as around only 50% of its content is absorbed. Even with all the information on prevention, the percentage of women who use pre-conceptional FA have not increased above 30%, coupled with the lack of attachment to the daily intake of vitamins and second to the lack of planning pregnancies. In Mexico, bottles of folic acid tablets are delivered during vaccination campaigns. However, they are not linked to a campaign of information and awareness of its benefits and how they should be consumed.

In Nuevo Leon, we developed a strategy in 2000 for the weekly consumption of 5 mg of FA, aimed at all women of childbearing age, regardless of whether they were planning to become pregnant or not, which achieved a 50% reduction in anencephaly cases and a 70% reduction in cases of spina bifida.⁶

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1665-5796/© 2017 Universidad Autónoma de Nuevo León. Published by Masson Doyma México S.A. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
But why has it not been possible to reduce cases of NTDs the world over, even with the knowledge that it can be reduced by up to 70%?

First, we have no culture of prevention of taking medication (here we would like to clarify that FA is not a medicine as such. It is a B vitamin) when we are not suffering from any particular condition. Second, most health staff does not know that FA must be taken at least three months before pregnancy to prevent NTDs. Third, the large number of unplanned pregnancies.

It is necessary to create an awareness of prevention, not only of adverse events during pregnancy, but many aspects of our health. In the case of congenital defects, folic acid makes the difference between a healthy baby and one with disabilities.

References


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Available online 2 June 2017
ORIGINAL ARTICLE

Laparoscopic training by use of a physical simulator and its application in the general surgery residency


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KEYWORDS
Laparoscopic physical simulator; Laparoscopic training; Decreased surgical time

Abstract

Introduction: Minimally invasive techniques have become the gold standard for a number of surgical procedures. The benefits include a decrease in morbidity, reducing the length of hospital stay and a faster return to daily activities.

Material and methods: An experimental, longitudinal, comparative, prospective, non-blinded study. A training program of 4 weeks’ duration was carried out with an experimental group of first and second year General Surgery residents and social service medical interns (group A); at the end of the training there was a test, where a series of exercises compared the residents who took the training program with a control group (group B) composed of residents from the fourth and fifth year who did not take this training.

Results: Upon analyzing the two groups, we observed a decrease in the average time by group A compared to group B. Overall, the 7 exercises show a difference in average time, with group A completing them in 5 min compared to group B’s 12 min (p < 0.05).

Discussion: This study shows that training in a physical simulator for laparoscopic surgery, for at least two hours a week for a month, is sufficient to improve laparoscopic surgical skills, reducing turnaround times by more than half compared to those who did not undergo this training.

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Introduction

Minimally invasive techniques have become the gold standard for a number of surgical procedures. Benefits include a drop in morbidity, thus reducing hospital stay, and a faster return to everyday activities.\(^1\)

The term ‘‘learning curve’’ was introduced in surgery to make a reference to the number of surgeries that a surgeon must perform in order to reach a level of experience with a low incidence of the range of complications. Depending on the type of surgery, between 15 and 100 procedures are required to reach the learning curve plateau. Even experienced laparoscopic surgeons have to go through the learning curve again when they train for new laparoscopic techniques or instruments.\(^2\)

For a long time, surgical teaching and training has been based on a teacher–student model, applied mainly in the operating room. In recent years, however, there have been major changes in surgery. Additionally, the available time for residents in their first years has shortened, and new surgical techniques have emerged. These new techniques lead to new and significant demands in surgical teaching and training, resulting in new methods to acquire experience and skills.

The use of a visual feedback base in monitors or other types of screens gives laparoscopy a wide range of teaching and training possibilities based on computing systems.\(^3\)

Intracorporeal knot-tying and suturing is amongst the most difficult tasks in laparoscopy, involving hand-eye coordination skills and knowledge of the proper steps. Proficiency in laparoscopic sutures is an important requirement for surgeons who wish to conduct advanced laparoscopy.\(^4\)

A non-randomized study showed a significant improvement in intracorporeal suturing by acquiring skills training in a laparoscopic training box.\(^5\)

There are virtual reality simulators or laparoscopic training boxes used for training,\(^6\) whose objective is the development of the necessary skills and understanding of the spatial-temporal frame of reference and required maneuvering to manipulate instruments and tissue in a bidimensional vision, camera manipulation and the ability to control instruments with both hands; thus being able to perform complicated surgical procedures with minimal invasion.\(^7,9\)

The objective of this study is to prove that applying a training program using a laparoscopic training box during a general surgeon’s residency will result in a shortening of time when performing laparoscopic techniques.

Material and methods

An experimental, longitudinal, comparative, prospective non-blind study was conducted. A 4-week training program was carried out at the Department of General Surgery of a teaching Hospital in northeastern México. The program included an experimental group of first and second-year general surgery residents, as well as interns doing their social service (group A). At the end of the training, a test was conducted where they performed a series of exercises comparing the residents who completed the training program with those in the control group (group B), which included fourth and fifth-year residents who did not complete said training. The program began with the completion of a laparoscopic skills test in a training box, where 7 exercises were performed, bimanual transference using beads toward a post, beads transfer from one container to another, predetermined cut, traction and counter-traction, simulation of intestine inspection using a string, and points of the suture with intracorporeal and extracorporeal knots. This practice was conducted for at least 2 h a week for 4 weeks. The exercises consisted of the following:

I. Intracorporeal knot: Two suture points will be done with a 4-lacing intracorporeal knot, the total time spent on this knot will be measured. Making an intracorporeal knot on a fixed surface is a common practice in laparoscopic surgery.

II. Beads 5/5: 10 beads will be placed (5 yellow and 5 blue) in a container at the center of the image, and there will be two posts, one on the right and another on the left of the container. Using the dominant hand, 5 beads of the same color will be placed on their opposite post, and with the non-dominant hand the rest of the beads which are a different color will be placed on the opposite post. The complete process will be timed from start to finish. This skill is required to perform fine movements and manage depth, necessary skills for staple placement.

III. Beads 10/10: Transfer 10 beads from one container to another using the dominant hand and return them to the first container using the non-dominant hand, the amount of time required to finish the exercise will be measured. This skill is necessary to perform fine movement and to moderate pressure strength similar to that required to extract lines from the abdominal cavity.

IV. Predetermined cut: A predetermined cut will be made (a circle in a piece of cloth) and the amount of time required to complete the circle will be timed. Skill required in the management of laparoscopic scissors with a single hand and presentation with the other hand is necessary for cuts in laparoscopic surgeries.

V. String: Simulation of intestine inspection using a meter-long string with 3 marks, measuring the amount of time it takes to reach the last one. Tests the ability to use both hands, as specified by the simulating intestine inspection.

VI. Grape decortication: An exercise in tension and strain relief will be made by decortication of a grape of medium size and the time required to completely peel it will be measured. This ability is required for the use of both hands, well-controlled use of force and pressure of the fine movements required for the detachment of ligaments and loose tissues and dissection and exposure of structures.

VII. Extracorporeal knot: A suture will be made with 4 extracorporeal knot loops and the time to finish is measured. Making an extracorporeal knot using the low knots is a common practice in laparoscopic surgery.

Upon completion of the four week training program, participants in the experimental group (group A) must have completed 90% of the previously specified hours (7.2 h) and have performed at least 90% of the indicated time periods. A comparative test was performed where residents of Group...
A and Group B performed the specified exercises, time was taken with a stopwatch, and the two groups’ times were compared at the end of the study.

Results

A total of 20 residents were analyzed, 10 in each group. 15 (75%) were male and 5 (25%) were female. The average age was 28 years. Upon analyzing the two groups, we observed a decrease in group A’s average time compared to group B’s average times (Table 1).

When comparing times, according to the exercise performed, we found the following: in exercise I (intracorporeal knot), there was a greater time difference shown between the two groups, and we found symmetry in subjects in group A and a slight asymmetry in subjects in group B. Exercise II (counts 5/5), was described by subjects as the most difficult. One subject in group B far exceeded the time achieved, on average, for the rest of the subjects in the same group. However, we observed an obvious decrease in group A’s average time. In Exercise III (10/10 accounts), a large difference was observed, where group A ended with an average of 4 min and group B ended with an average of 7 min. Exercise IV (default cut) shows the clear time difference between the two groups, where group A has a shorter time. Exercise V (string), shows that this exercise had the shortest time for the two groups. In group A, there was no decrease in time, with symmetry subjects, contrary to group B, where it took longer and there is asymmetry. Exercise VI (decorticating grape), less time is observed in group A. Exercise VII (low knot knots), shorter time is observed in group A compared to group B, and the latter showed more asymmetry between subjects.

These 7 exercises together show a lower average time difference in group A with 5 min, compared to group B with 12 min, p < 0.05 (Figs. 1 and 2).

Therefore, we stress that exercise II presented greater difficulty, showing increased consumption of time, and exercise number V shows the least difficulty. Of the 7 exercises, we can observe a difference in the performance time in both groups, with significant differences (Table 2).
Discussion

There is a homogeneity between the two groups with regard to distribution by age and gender. The study involved a total of 20 subjects, 10 were subjected to training two hours a week for four weeks, and finally, were subjected to the application of the 7 exercises mentioned in Table 1, while the other 10 only underwent the implementation of the 7 exercises already mentioned. A considerable time difference was demonstrated in the performance of laparoscopic tasks between the two groups. We found that, of the seven tasks applied and measured, exercise II, where the subjects must place 5 beads of the same color on their opposite post and vice versa, as presenting the greatest difficulty to implement, and exercise V, mobilization of the string, as the simplest, as can be seen in Table 1. At the end, we obtained significant statistical $p$ values in the 7 exercises between the two groups.

In a German study, which involved eight expert surgeons and 24 rookies (inexperienced medical students), in which they performed exercises on two physical laparoscopic training simulators, a virtual endoscopic surgery trainer, and a conventional video training device, both groups showed improvement in their times upon completion of their training, as opposed to at the beginning. However, the skilled surgeons had the best times in all exercises, unlike our study, where those who underwent the laparoscopic training without previous experience had better times.

In another study in Australia with 26 participants involving the use of a conventional laparoscopic simulator compared to a virtual simulator, greater consistency in learning was observed with the conventional laparoscopic simulator, which was also used in our study so that we could provide a good training tool.

In a study conducted in Spain with a laparoscopic simulator, it was observed that the residents’ level of confidence in the practice of laparoscopic procedures after completion of training increased by 70%, thus, just as in our study results in better surgical times.

Conducting training in laparoscopic surgery skills with a physical simulator significantly reduces turnaround times in the tasks involved in such procedures. It showed that training in a physical laparoscopic surgery simulator, for at least two hours a week for a month, is sufficient to improve laparoscopic surgical skills and reduce turnaround times by more than half compared to the times of those that do not undergo the training. This lead us to believe that, as the surgeon undergoes more training from the early stages of his residency in general surgery, he will be able to show a better perform with safer skills when met with the situation of performing a laparoscopic procedure on a living person.

**Table 2** Descriptive analysis between the two groups according to performance times.

<table>
<thead>
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<th>Group</th>
<th>$N$</th>
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<th>Standard deviation</th>
<th>Standard error of the mean</th>
<th>$p$</th>
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<td>Age</td>
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<td></td>
<td></td>
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<td>Group A</td>
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<td>28.200</td>
<td>2.2509</td>
<td>0.7118</td>
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<tr>
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<td>10</td>
<td>27.300</td>
<td>1.3375</td>
<td>0.4230</td>
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<td>I – Intracorporeal knot</td>
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<td></td>
<td></td>
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<tr>
<td>Group A</td>
<td>10</td>
<td>0:05:41.96</td>
<td>0:00:49.734</td>
<td>0:00:15:727</td>
<td>&lt;0.05</td>
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<td>10</td>
<td>0:17:17.38</td>
<td>0:02:29.706</td>
<td>0:04:47.341</td>
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<td>II – Beads 5/5</td>
<td></td>
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<td>Group A</td>
<td>10</td>
<td>0:07:18.19</td>
<td>0:01:37.520</td>
<td>0:00:30:839</td>
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<td>Group B</td>
<td>10</td>
<td>0:18:35.68</td>
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<tr>
<td>Group A</td>
<td>10</td>
<td>0:03:41.24</td>
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<td>IV – Predetermined cut</td>
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<td>Group A</td>
<td>10</td>
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<td>V – String</td>
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<td>10</td>
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<tr>
<td>Group A</td>
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<td>0:06:45.16</td>
<td>0:00:38:811</td>
<td>0:00:12:273</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Group B</td>
<td>10</td>
<td>0:15:53.26</td>
<td>0:01:47:945</td>
<td>0:00:34:135</td>
<td></td>
</tr>
<tr>
<td>VII – Extracorporeal knot</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group A</td>
<td>10</td>
<td>0:02:27.32</td>
<td>0:00:38:281</td>
<td>0:00:12:106</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Group B</td>
<td>10</td>
<td>0:06:42.71</td>
<td>0:01:17:983</td>
<td>0:00:24:660</td>
<td></td>
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<td>Average</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Group A</td>
<td>10</td>
<td>0:04:26.20</td>
<td>0:00:25:227</td>
<td>0:00:07:978</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Group B</td>
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<td>0:11:22.73</td>
<td>0:00:44:008</td>
<td>0:00:13:917</td>
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</tbody>
</table>

![Figure 2](image-url)  
**Figure 2** Comparison of both groups by exercise.
thus achieving a reduction in the risk of complications arising from a lack of technique or skills in this type of procedure. Yet we must always keep in mind that physical simulators for laparoscopic training are just a tool to enhance one’s ability, and must never replace training and experience in actual surgery assisted by teachers and expert surgeons.

Conflict of interest

The authors have no conflicts of interest to declare.

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Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

References

ORIGINAL ARTICLE

Tumor Necrosis Factor alpha, prognosis and stroke subtype etiology

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KEYWORDS
TNF alpha;
Cerebral stroke;
Lacunar infarction;
Atherosclerosis

Abstract
Objective: To determine the relationship between TNF alpha and the etiology, localization, extension, intima media thickness, carotid atherosclerotic plaque, and outcome after an acute stroke.

Methods: We randomly selected 75 patients with acute strokes from a total of 253 patients that were admitted prospectively from May, 2008 to December, 2010. We analyzed TNF alpha levels and compared it with demographic data, clinical outcome upon hospital discharge, and at 3 months post discharge with neuroimaging studies. We used the Chi-square test, the U-Mann–Whiney test and the Cox logistic regression adjusted for age, gender and stroke extension.

Results: We included 47 men and 28 women. The most common etiologies were atherosclerotic (39%) and small vessel disease (27%). TNF alpha levels did not differ between atherosclerotic and cardioembolic stroke etiologies, except for the lacunar infarction, which had the lowest levels (p = 0.048), and did not correlate with a worse functional outcome upon hospital discharge (p = 0.852) or at 3 months following discharge (p = 0.194). Additionally, we found a positive relation between intima media thickness >1 mm and TNF alpha (p = 0.004). TNF alpha was not associated with the extension of the stroke by an ASPECTS score with CT or MRI (p = 0.323) or with the arterial territory involved (p = 0.289).

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Introduction

Strokes are the most common cause of functional disability in adults\(^1\) and the sixth leading cause of death in our country.\(^1\) It is considered to be the second most common cause of death in the world, and its prevalence is increasing in developing countries due to increased life expectancy and changes in eating habits and lifestyle.\(^1\)

A stroke may have different etiologies. Among them, the most common are known to be large artery atherosclerosis, small vessel disease or lacunar type, and caused due to cardiac embolism.\(^2\) Other less common causes are pro-thrombotic states of systemic diseases, primary or secondary cerebral vasculitis, and arterial dissection secondary to medications or harmful substances.\(^3\) When a patient has two probable causes or there is a failure to clarify the etiology, it is defined as undetermined until the moment that its origin is detected. Up to 15–25% of strokes remain undetermined.\(^1\)

Atherosclerosis is a more common cause, especially in adults older than 50 years.\(^4\) Unfortunately, there are no reliable statistics on the prevalence of atherosclerotic carotid artery stenosis in strokes in our country. However, in other developed countries, it has been established that 35–50% of cases are caused by atherosclerosis of large vessels, such as the carotid artery, the thoracic aorta, and the proximal intracranial vessels.\(^3\)

The second most common cause of a stroke is a disease of the penetrating vessels by degeneration of the vascular wall or lipohyalinosis, with the consequent microangiopathy of the small cerebral vessels and infarcts of a more limited volume, usually less than 1.5 or 2.0 cm.\(^4\) This disease is typical of patients with hypertension and/or chronic diabetes. The volume of injuries from a lacunar infarct is small; therefore, a lesser number of neurons are affected. However, its clinical consequences depend on the location of the lesion.

Thirdly, there is the cardio-embolic etiology. This may be due to an arrhythmic phenomenon, or an injury to the heart wall that conditions a focal myocardial dyskinesia and thus the formation of an intracavitary thrombus, as occurs after a heart attack.\(^5\) Although more common in younger subjects, its diverse etiology makes it likely in the elderly as well. Strokes, as a consequence of an embolus from the heart, can hide a distal artery in the brain, and generally hide a vessel of great size, leading to a wide-reaching stroke.\(^3\)

The etiology may vary according to the study population, which is what makes it important to emphasize the etiological definition of a stroke in all prospective cohorts of patients.

After a stroke, inflammatory phenomena as a result of the damage and its extent occur,\(^4\) as well as others, which seek to limit the consequences of the lack of irrigation in the peripheral area of a stroke, known as the ischemic penumbra area.\(^5,6\)

Among the molecules that have been defined to be associated with strokes, their extension and prognosis, are cytokines, such as IL-1, IL-6, and TNF alpha.\(^7\) Some molecules increase in blood immediately and remain in the blood at high levels for several days. Their quantification may be a reflection of the degree of damage or the extent of the stroke, and may even help to etiologically differentiate the type of stroke.\(^5,6,8-10\)

Tumor Necrosis Factor (TNF) alpha and Cerebral Vascular Disease (CVD)

TNF alpha is produced by brain cells, both neurons and microglia, after suffering ischemia.\(^11\) It is involved in all stages of brain injury by stroke. Its pro-inflammatory effect appears to initially maintain cerebral flow in the periphery of the stroke and is proportional to stroke size.\(^3,5-9\)

Many studies that have associated etiological subtype and functional prognosis following a stroke, but few who have studied TNF alpha as a pro-inflammatory cytokine cerebral spinal fluid and serum that can be associated with the size, clinical severity and etiology of a stroke.\(^4,5,8-10,12-14\)

In a study of 123 stroke patients and 123 healthy controls, patients with cardioembolic CVD showed higher levels of TNF alpha plasma in plasma when compared with the other subtypes.\(^13\) In a study of 36 patients with acute ischemic stroke at admission, it was found that concentrations of TNF alpha did not vary significantly from controls, but the amount of soluble TNF receptor type 1 in the first week correlated strongly with stroke size by CT at 5–7 days, as well as the mRS (modified Rankin Scale) at 3 and 12 months.\(^11\)

There have only been a few studies on the behavior of TNF alpha in strokes, especially TNF alpha in acute strokes that emphasize the stroke etiological subtypes and clinical features.

Materials and methods

Patients

This is an analytical cross-sectional study nested in a prospective cohort of patients diagnosed with a stroke who were admitted to the Neurology Department at a tertiary level teaching hospital in Northeastern Mexico (Intrahospital Registry of NeuroVascular Disease – IRENE-) in the period of May, 2008 to December, 2010. The protocol was approved by the Ethics Committee; patients and/or family members signed a letter of consent.

Conclusions: TNF alpha was not globally associated with functional outcome after acute stroke, just in the lacunar infarction, which has the lowest levels. We also found a positive relation between TNF alpha and intima-media thickness.
During the aforementioned period, 253 patients with a diagnosis of cerebrovascular disease were hospitalized. 75 patients were chosen at random from a selection of 133 patients with a confirmed stroke diagnosis, with complete imaging studies, laboratory and clinical follow-up at hospital discharge and at 3 months.

Demographic information, etiology, stroke location and laboratory and imaging studies were obtained from the form used by the Neurovascular Care Room since 2008. The extent of the stroke was determined by the ASPECTS (Alberta Stroke Program Early CT Scan) scale, by CT or by MRI. All patients' functional status was measured with modified Rankin and NIHSS (National Institutes of Health Stroke Scales) scales upon admission, hospital discharge and during a follow-up at 3 months, either by outpatient or phone call using the validated Rankin telephone tool. Among the comorbidity background, we included a sedentary lifestyle (lack of routine exercise for at least 30 min a week in the last 6 months) and cardiovascular disease (history of angina pectoris, myocardial infarction, heart failure or valve disease).

Serum samples were taken by venipuncture between day 0 and day 16 of hospitalization. 56% of the samples were taken in the first 48 h. Samples were stored at −80 °C in our Department of Biochemistry of the School of Medicine.

### Functionality scales in CVD

The use of standardized functional scales is essential to compare populations of different origins. The mRS is a comprehensive clinical evaluation of disability. It consists of degrees from 0 to 6, with 0 being an asymptomatic patient, grade 5 being a patient that requires full support 24 h a day, unable to perform the most basic activities, and 6 describes a deceased patient. A simplified mRS questionnaire has demonstrated excellent reproducibility and reliability when applied by telephone.16,17

The NIHSS are widely used and validated to assess severity. In the acute phase of a heart attack, it is a powerful predictor of the final clinical outcome.18

The ASPECTS scale determines changes in ischemia on CT. The value is obtained from 2 axial cuts. It divides the territory of the middle cerebral artery into 10 regions, and one point for each affected area is subtracted. It is related inversely with the severity of the stroke. A lower value of 7 is associated with increased reliance and the risk of death at 3 months. In a study of the ability to detect early ischemic changes, ASPECTS was similar to CT and MRI in diffusion sequences.17

### Analysis of TNF alpha

After obtaining the blood samples, they were centrifuged and the plasma was separated. They were taken to the Department of Biochemistry in our School of Medicine, where they were stored frozen. The samples were thawed and measurement of TNF alpha was performed with the conventional technique using commercial Milliplex Map kits. Measurements were performed at the laboratory at a tertiary level teaching hospital in Northeastern Mexico.

### Statistical analysis

A descriptive analysis of the population's demographic and clinical variables was made. The dependent variable for functional status at discharge and at 3 months was obtained through a dichotomized modified Rankin scale with a good prognosis (0–3) and a poor prognosis (4–6). Comparisons were made with Pearson’s Chi-square tests (or Fisher’s exact) for contingency tables, or the Mann–Whitney U test for comparison against quantitative or qualitative non-parametric variables, as appropriate.

TNF alpha values were analyzed with the Kolmogorov-Smirnov normality test to learn their distribution, and further analyzed in continuous values for Spearman correlation tests. 75 percentile values were taken to contrast with the patients’ clinical characteristics, stroke location and extent, and the presence of atherosclerosis, as well as their etiology and prognosis.

Finally, the variables that were significant in their association with the stroke prognosis underwent a multivariate logistic regression model along with the TNF alpha values. \( p < 0.05 \) was used as statistical significance, and we used the SPSSv.15 statistical program.

### Results

Seventy-five patients were randomly selected for this study, from 133 patients with the complete information required upon admittance and at the clinical follow-up 3 months after discharge.

The mean age was 12.9 ± 65 years (29–91 years old); 63% male and 37% female. The prevalence of comorbidities is shown in Graph 1. Of these patients, 96% had functional independence prior to their cerebrovascular event.

Time of arrival after the start of symptoms was <3 h in 10.6%, 3–6 h in 17.3%, 6–24 h in 45.3%, 1–7 days in 25.3% and >7 days in 1.3%.

Regarding etiology, 39% were atherothrombotic, 27% were due to small vessel disease (lacunar infarcts), 15% to cardioembolism and the etiology could not be determined, or more than one possible etiology was found, in 20%.

The thickness of the carotid intima-media in the common carotid artery was determined for all patients via Doppler ultrasound, finding an average value of 0.930 ± 0.303 mm (0328–2672). 68% of patients had carotid atherosclerotic plaques (greater than 30% stenosis), and we found an association between the presence of plaque and age \( (p = 0.036) \) as well as with a history of diabetes mellitus \( (p = 0.028) \).

Regarding vascular infarct location, the middle cerebral artery region was the most frequent (62%), followed by the vertebrobasilar region (20%), the anterior cerebral artery (6.6%), and the carotid artery (6.6%).

Upon arrival at the emergency room, the patients' score on the NIHSS were determined. An NIHSS score of 22.6% presented between 0 to 4 points (mild stroke), 54.6% presented an NIHSS score between 5 to 12 points, and 22.6% presented an NIHSS score higher than 13 points. Their score was re-evaluated upon entering the Neurology Department, where 24% scored 0–4, 58.6% scored 5–12 and 17.3% scored greater than 13.
Upon hospital discharge, after an average stay of 8.5 days (range 2 to 32 days), an mRS showed 62.6% of patients between 0 and 3, 32% between 4 to 5 points and death (mRS = 6) in 5.3%. Upon hospital discharge, their NIHSS score was between 0 and 4 points on 48% (mild sequelae), between 5 and 12 points on 36% (moderate scale) and was higher than 13 in 16% of patients (disabling sequelae). At the 3-month follow-up, only the modified Rankin test was performed, which showed a score of 0–3 (functional independence) in 50.6%, 4–5 in 36% (functional dependence) and death (mRS = 6) in 13.3%.

Regarding the extent of their strokes, we found an average value of 8.2 points, with a range of 6–9 points, on the ASPECTS scale (Fig. 1).

There were differences in the results between associations of neurological recovery and the etiological type of stroke depending on the functional scale evaluated, with the small vessel disease or lacunar infarct having lower scores on the NIHSS scale, and therefore less neurological damage (p = 0.044). On the other hand, with the modified Rankin scale, the etiology with the poorest prognosis at discharge was atherothrombosis (p = 0.041) and the small vessel disease had the best functional prognosis again, i.e., lower mRS values (p = 0.003).

At 3 months, the etiology with the poorest prognosis was cardioembolic (p = 0.001), and the etiology with the best prognosis was small vessel disease (p < 0.0001).

**Tumor Necrosis Factor alpha**

TNF alpha values averaged 6 pg/ml with a range of 0.79–17.38 pg/dl. The values differed according to the etiology of the stroke. The average values of TNF alpha are shown in Table 1. Lacunar infarcts were associated with lower levels of TNF alpha (p = 0.048). Glucose levels on admission were not related to TNF alpha (p = 0.545).

Regarding atherosclerosis, a significant association between a thickening of the intima media (greater than 1 mm) and the levels of TNF alpha (p = 0.004) was found. However, the presence of an atherosclerotic plaque greater than 30% was not related to TNF alpha (p = 0.625).

TNF alpha levels were not found to be associated with the extent of the strokes, even eliminating the lacunar infarctions (p = 0.323), which suggests an association with

![Graph 1 Prevalence of comorbidities (background) in the study population.](image)

**Table 1** Tumor Necrosis Factor (TNF) alpha values by etiological stroke group.

<table>
<thead>
<tr>
<th>Etiology</th>
<th>TNF alpha (pg/ml)</th>
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</thead>
<tbody>
<tr>
<td>Atherothrombotic, n = 29 (39%)</td>
<td>6.13 (0.9–17.38)</td>
</tr>
<tr>
<td>Small vessel disease (lacunar infarction), n = 20 (27%)</td>
<td>4.79 (0.91–16.12)</td>
</tr>
<tr>
<td>Cardioembolism, n = 11 (15%)</td>
<td>7.37 (1.75–13.99)</td>
</tr>
<tr>
<td>Indeterminate origin, n = 15 (20%)</td>
<td>6.64 (1.96–15.56)</td>
</tr>
</tbody>
</table>

* Defined as a stroke with two possible causes or without an etiological definition despite conventional study.

TNF alpha regardless of infarct size. Similarly, there was no relationship between infarct location and TNF alpha levels (p = 0.289).

Low levels of TNF alpha were not associated with a better prognosis at hospital discharge, or with the modified Rankin Scale (mRS 0–3; p = 0.852), and only marginally with the group of patients with a lower NIHSS score (from 0 to 4; p = 0.059).

As for their prognosis at three months, measured by the telephone mRS, no association was found with TNF alpha levels at admission (p = 0.194).

**Discussion**

TNF alpha is produced by brain cells after suffering ischemia and some authors have associated it with a worse functional prognosis.

In our study, TNF alpha levels were not related to functional outcome at hospital discharge, and very discretely at 3 months with the NIHSS scale. This is possibly due to the small number of cases in the study, and also may be because the prognosis of the target population for this study was generally good, with a functional recovery of 84%, according to the Rankin scale.

Stroke by small vessel or lacunar disease is the second leading cause of strokes in our hospital (19%), and its etiology is defined until we can make a correlation between cardiovascular risk factors, clinical manifestations and findings in brain imaging studies, such as MRI.
Patients with a stroke due to small vessel disease had lower levels of TNF alpha, and better outcomes at hospital discharge and at 3 months. This could be assumed to be due to having strokes of smaller size. However, upon analyzing the ASPECTS scale for stroke size and levels of TNF alpha, no association was found. Small vessel or lacunar disease generates the least cytotoxic edema, besides being the stroke with fewer affected cells. This could be useful, since the determination of TNF alpha levels in pre-hospital care would help predict the lacunar subtype of stroke and hence lower ischemic penumbra, with no need for an endovascular approach, and a better prognosis. In addition, lacunar infarction is not accompanied by a demonstrable arterial occlusion in imaging studies such as CT angiography or a magnetic resonance angiography, which predicts a good response to an intravenous thrombolytic drug.

Other authors have found that TNF levels correlate with stroke volume. In our population, the ASPECTS scale scores were very similar, possibly caused by not having the dispersion of the values necessary to find a significant difference.

Interestingly, we discovered an association between TNF alpha levels and the presence of thickening of the carotid intima-media greater than 1 mm, and not with the occurrence of atherosclerotic plaques in the carotid arteries, which suggests that the intima media thickness is a factor independent to plaque formation, similar to what others have suggested.22

Figure 1 Outline of the division of the territory of the middle cerebral artery into 10 regions for the ASPECTS scale (less of 7, means more than 1/3 of the artery territory involved).

Fifty-two percent of the samples were taken, centrifuged and frozen within 48 h of admission, and 91% in the first five days, a time when others have seen the largest increase in concentrations of TNF alpha or its receptor occurs.

In our study population, high glucose levels at admission had no influence on the patients’ prognosis; even the highest levels, at 180 mg/dl, were associated with a good prognosis at the follow-up 3 months after the acute event.

Hospital mortality was 5.3%, and mortality was 13.3% at 3 months. This is less than the 16% mortality rate in the first month reported in the literature.23 But this may be related to the fact that our chosen group had fewer patients with very extended strokes.

Almost half of our patients came for medical care within 6 to 24 h after symptom onset and only 10.6% arrived within 3 h, so the chances of thrombolytic treatment were very few. Of the 8 patient candidates, only 3 received thrombolytic treatment.

Cardiac ischemia studies have consistently found a significant difference between TNF alpha levels and cardiovascular prognosis.7 On the other hand, results in strokes have been mixed. There are reports in the literature of a significant association between stroke prognosis and TNF alpha levels,5,8 while others have found no association,7 or just a trend,12 and there are even those who report an opposite effect and a protector of pro-inflammatory cytokines.10

This may be because the stroke, unlike the other vascular pathologies, such as cardiac, has diverse etiologies. That is why it is important to define its causes via cohort studies, including the study of prognostic biomarkers.

Welsh et al. demonstrated an association between TNF alpha levels and the risk of recurrent heart attacks, and emphasized that it only occurs in those with very high concentrations of TNF alpha (> 2.89 pg/ml). In our population, the percentage of patients whose levels of TNF alpha were found to be above these values was very high (66%), with a maximum value of 17.38 pg/ml and an average value of 6 pg/ml. Despite this, the overall prognosis for our group at 3 months was good. This could be due to the fact that we had a significant percentage of lacunar infarcts (27%), with a good prognosis and lower TNF alpha concentrations.

Like other studies,13 we found that patients with cardioembolic etiology have worse outcomes, and that patients with CVD by small vessel disease are those with a better prognosis, being no relationship observed with the first to TNF alpha levels, since those values were indistinguishable from those by atherothrombotic causes or unknown causes.

This relates to the findings of Licata et al.,12 where it was observed that patients with cardioembolisms show a greater
inflammatory response associated with an increase in TNF alpha, hence worsening the evolution.

In this group of patients, their strokes showed an average of 8 on the ASPECTS scale, with the largest showing values of 6. However, there were few cases of strokes with values less than 7, a cutoff value related to prognosis in other studies. It is likely that the lack of association found between TNF alpha levels and stroke size is because bigger strokes were not presented.

Our study had several limitations. (1) The reduced number of patients selected for this sample could interfere with the lack of association between TNF alpha levels and prognostic variables in the functional scales. However, the association between TNF alpha values and lacunar infarct subtypes is similar to other authors, and the population was randomly selected in order to reduce the sample size and thus the cost of laboratory studies. (2) Follow-up at 3 months was made by phone. This could have interfered with our results. However, the survey was made via a validated telephone Rankin scale which is used routinely by our Service. (3) Strokes with an undetermined etiology were included. Strokes with an undetermined etiology probably arise due to the fact that sometimes not all necessary diagnostic studies are performed, either due to a lack of funds or a lack of adherence to outpatient follow-up. However, since the creation of the database on stroke and systematic registration in the Neurovascular Care Unit in the Department of Neurology, we have reduced this percentage significantly.

Conclusions
Small vessel disease had significantly lower levels of TNF alpha, while other etiologies were unrelated. However, they were not associated with better functional prognosis at hospital discharge and at follow-up in 3 months. An association between higher levels of TNF alpha and carotid intima-media thickness of more than 1 mm was found. More prospective studies are needed with larger numbers of patients to validate these results. Its routine use in prehospital evaluation could be useful in deciding whether or not the patient should move to a neurovascular unit with or without endovascular therapy intervention.

Ethical disclosures
Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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Conflict of interest
The authors have no conflicts of interest to declare.

References


ORIGINAL ARTICLE

The College Adjustment Scales (CAS) test and recent students’ school performance upon entry into a medical school

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KEYWORDS
Psychometric tests; Dropout; Depression; Suicidal ideation; Academic performance; Vocation

Abstract Admission to a degree program represents a challenge for new students, which those that show greater emotional stability and ability to face school adjustment will best solve. The Draw a Person test and Anton and Reed’s College Adjustment Scales (CAS) questionnaire was applied to 2364 first year students of a Medical School in northeastern México admitted during the years 2013 and 2014. One or more abnormal scales were documented in 674 students (28.4%). A correlation study between 1000 students with normal scales and the 674 students with abnormal scales was performed. The group with normal tests had a greater number of student approval (64% vs 46.9%) \( p = 0.03 \). A significant correlation was found with school failure in four of the CAS abnormalities: depression (\( p = 0.005 \)), academic problems (\( p = 0.001 \)) substance abuse (\( p = 0.004 \)) and suicidal ideation (\( p = 0.043 \)). We concluded that the evidence of depression, academic problems, substance abuse and suicidal ideation were associated statistically with low academic performance in the study population.

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Introduction

Academic performance is defined as the fulfillment of the goals, accomplishments, or targets set in the program or course in which a student is enrolled. One of the problems
of greatest interest in higher education in Mexico is the high dropout rate of students. The period in which the largest percentage drop occurs happens in the early years of their university career periods, especially critical because young people are in a new evolutionary stage, known as emerging adulthood. This stage is characterized by high instability, anxiety, and the seeking and exploration of identity. Access to higher education in this stage of development brings new social problems to young people, such as separation from family and friends, creating new friendships, and demands for greater autonomy. The effects of these changes, as well as increasing academic demands, hinders successful adaptation to the university and is a condition for successful permanence in it. Recent studies highlight social support as one of the most important protective factors against disturbing or adverse experiences arising from incorporation into the university. There are two essential aspects of social support: the perception that you have a number of people who can be called upon in case of need and satisfaction with that support. Some students require the support of a greater number of people to show satisfaction, while for others the support of one person is enough. In this study, adaptation to the university was studied using the questionnaire known as the College Adjustment Scale (CAS) developed by Anton and Reed in 1991, and the Draw a Person test by Machover.

**Objective**

Understand the students’ capacity to adapt to the university environment upon entering of a Medical School in northeastern México and determine if there is a statistical relationship with school failure.

**Material and methods**

The Anton and Reed CAS questionnaire and Machover’s Draw a Person test was applied to 2250 (95.2%) students in the admission process to the School of Medicine and 114 (4.8%) in the Clinical Laboratory Sciences (CLS) for a total of 2364 students. The CAS has 108 reagents, divided into nine adjustment scales: anxiety, depression, suicidal ideation, substance abuse, self-esteem, interpersonal problems, family problems, academic problems and problems in vocational career choice. The students answered on the basis of four points: 1 (totally false); 2 (often false); 3 (almost always true); and 4 (totally true). Each of the nine scales consists of 12 questions, with a minimum score of 12 and a maximum score of 48. The highest results indicate low settings and the lowest results mean better adjustment. The test was translated, standardized and adapted to the population of medical students from the classes that joined in August, 2013, February, 2014 and August, 2014. The results were normal for 1690 (71.5%) students, and 674 (28.4%) had one or more abnormal results. The Machover test, or the Draw a Person test, was assessed based on a rating of 1–5, with 1–3 being normal and 4–5 being abnormal. A representative sample of students with normal results (1000–1690) was taken, and all students with abnormal results (674) were correlated with their academic performance, taking as a basis an average of 70 or more obtained during their semester. Statistical analysis included: descriptive frequency analysis, Pearson correlation index, p-value, χ² test, and estimation of relative risk.

**Results**

The number of male students was 1335 (56.5%) and 1028 female students (43.5%) were included in this study. Normal results were documented in 1690 students (71.5%) and abnormal results in one or more of the scales in 674 (28.4%). Distribution and percentage of scales that were abnormal can be seen in Table 1. In six of the scales, a difference was found by gender as follows: depression (62.5%), anxiety (60.8%), family problems (60%) and self-esteem (59.1%) were more frequent in women, and abnormalities in substance abuse (67.6%) and the Machover test (73.9%) were the most prevalent among men (Table 2). Considering the passing grade with a value of 70, we found that in the group with normal results on their tests, a total of 640 respondents passed (64%) and 360 flunked (36%), and in the group of students with abnormal CAS scores, 316 students passed (46.9%) and 358 flunked (53%), with a difference of p < 0.01 (Table 3). The correlation of the results of the CAS scales with the average grades achieved during the first semester showed a statistically significant relationship with 4 scales: depression, academic problems, substance

---

### Table 1  Distribution of CAS scales and altered Machover tests in 674 students of the School of Medicine.

<table>
<thead>
<tr>
<th>CAS scales</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Academic problems</td>
<td>141</td>
<td>9.73</td>
</tr>
<tr>
<td>Anxiety</td>
<td>97</td>
<td>6.69</td>
</tr>
<tr>
<td>Interpersonal problems</td>
<td>110</td>
<td>7.59</td>
</tr>
<tr>
<td>Depression</td>
<td>88</td>
<td>6.07</td>
</tr>
<tr>
<td>Vocational problems</td>
<td>132</td>
<td>9.10</td>
</tr>
<tr>
<td>Suicidal ideation</td>
<td>89</td>
<td>6.14</td>
</tr>
<tr>
<td>Substance abuse</td>
<td>244</td>
<td>16.8</td>
</tr>
<tr>
<td>Self-esteem</td>
<td>191</td>
<td>13.18</td>
</tr>
<tr>
<td>Family problems</td>
<td>150</td>
<td>10.35</td>
</tr>
<tr>
<td>Machover</td>
<td>207</td>
<td>14.2</td>
</tr>
<tr>
<td>Total</td>
<td>1449</td>
<td>99.84</td>
</tr>
</tbody>
</table>

### Table 2  CAS scales and altered Machover tests by gender.

<table>
<thead>
<tr>
<th>CAS scales</th>
<th>Females</th>
<th>Males</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>Anxiety</td>
<td>59</td>
<td>60.82</td>
<td>38</td>
</tr>
<tr>
<td>Self-esteem</td>
<td>113</td>
<td>59.16</td>
<td>78</td>
</tr>
<tr>
<td>Family problems</td>
<td>90</td>
<td>60.00</td>
<td>60</td>
</tr>
<tr>
<td>Substance abuse</td>
<td>79</td>
<td>32.37</td>
<td>165</td>
</tr>
<tr>
<td>Suicidal ideation</td>
<td>46</td>
<td>51.68</td>
<td>43</td>
</tr>
<tr>
<td>Academic problems</td>
<td>63</td>
<td>44.68</td>
<td>78</td>
</tr>
<tr>
<td>Vocational problems</td>
<td>59</td>
<td>44.69</td>
<td>73</td>
</tr>
<tr>
<td>Interpersonal problems</td>
<td>60</td>
<td>54.54</td>
<td>50</td>
</tr>
<tr>
<td>Depression</td>
<td>55</td>
<td>62.50</td>
<td>33</td>
</tr>
<tr>
<td>Machover</td>
<td>54</td>
<td>26.08</td>
<td>153</td>
</tr>
<tr>
<td>Total</td>
<td>678</td>
<td>46.79</td>
<td>771</td>
</tr>
</tbody>
</table>
Do not hallucinate.

Table 3 Relation between normal and abnormal CAS results in 1674 passing and failing students.

<table>
<thead>
<tr>
<th>CAS test</th>
<th>Passed</th>
<th>Failed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>Normal</td>
<td>640</td>
<td>64.0%</td>
</tr>
<tr>
<td>Abnormal</td>
<td>316</td>
<td>46.9%</td>
</tr>
</tbody>
</table>

* p = 0.01.

Table 4 Correlation between CAS scales and Machover tests with school performance.

<table>
<thead>
<tr>
<th>CAS scales</th>
<th>p Value</th>
<th>OR</th>
<th>IC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression</td>
<td>0.005</td>
<td>1.89</td>
<td>1.21-2.96</td>
</tr>
<tr>
<td>Academic problems</td>
<td>0.001</td>
<td>2.04</td>
<td>1.36-3.05</td>
</tr>
<tr>
<td>Substance abuse</td>
<td>0.004</td>
<td>1.49</td>
<td>1.13-1.95</td>
</tr>
<tr>
<td>Suicidal ideation</td>
<td>0.043</td>
<td>1.59</td>
<td>1.02-2.47</td>
</tr>
<tr>
<td>Anxiety</td>
<td>0.136</td>
<td>1.37</td>
<td>0.90-2.09</td>
</tr>
<tr>
<td>Interpersonal</td>
<td>0.618</td>
<td>1.10</td>
<td>0.75-1.64</td>
</tr>
<tr>
<td>Vocational</td>
<td>0.515</td>
<td>0.87</td>
<td>0.60-1.26</td>
</tr>
<tr>
<td>Family problems</td>
<td>0.349</td>
<td>1.19</td>
<td>0.83-1.73</td>
</tr>
<tr>
<td>Self-esteem</td>
<td>0.115</td>
<td>1.30</td>
<td>0.93-1.81</td>
</tr>
<tr>
<td>Machover</td>
<td>0.470</td>
<td>1.22</td>
<td>1.00-1.48</td>
</tr>
</tbody>
</table>

* Statistically significant.

abuse and suicidal ideation. Academic problems showed the greatest risk (OR = 2.04, p < 0.001), followed by depression (OR = 1.89, p < 0.005), substance abuse (OR = 1.49, p < 0.004) and suicidal ideation (OR = 1.59, p < 0.043) (Table 4).

Discussion

One of the problems of greatest interest in higher education in Mexico is the high failure rate of its students. The CAS (The College Adjustment Scale) questionnaire, created by Anton and Reed in 1991, can quickly assess some problems that can affect adaptation to the university environment. In this study, four scales correlating significantly with low student learning were found: depression, academic problems, substance abuse and suicidal ideation. All of them associated with common etiological factors such as stress and the inability to adapt, low self-esteem and emotional deprivation.

Depression is a serious problem in university students. The university environment presents many goals and challenges, which the student must learn new skills. Students, when they are depressed, experience poor concentration, pessimism, low self-esteem and loss of energy. It is estimated that depression affects up to 30% of students in the university population, and 15% experience clinical levels of depression. Depressed students have more problems with college work and low motivation. Depression is more common in women and is related to low self-esteem, emotional and behavioral problems, as well as difficulties in academic performance. The use of alcohol and other drugs in adolescence has increased in Mexico in recent years and is the subject of social concern. The cause of substance abuse in adolescence is very complex, involving the deficit in the process of decision making, the negative influence of peers and adults who act as role models, the adolescent’s emotional deprivation and the distance from their family. Among the problems arising from the use of substances are not only their schooling, but also unplanned pregnancies, sexually transmitted diseases, and legal problems. Botvin showed that by avoiding adolescents’ exposure to illicit substances, we can reduce absenteeism and improve school grades compared to a control group. Suicidal ideation in adolescence is frequent, and usually comes from stress, which has a detrimental psychological and physical effect, including as a factor that triggers or exacerbates various symptoms such as low tolerance to frustration, anxiety, depression, fear, etc. Perez-Amezua et al. studied 14,306 students from 149 schools and found that nearly half of students in upper secondary education in Mexico had suicidal thoughts and that 9% had attempted suicide. Among the predisposing factors were sexual abuse, depression and consumption of snuff and drugs. Jiménez, and González-Forteza Mondragon, also in Mexico, found that the risk of suicidal ideation is higher in women, twice as much in relation to men, when they have low self-esteem, the risk increases by four times, and if there are depressive symptoms, the risk is thirteen times higher. In our study, we found no gender difference on this scale.

On the scale of academic problems, the students’ previous experiences in this area were analyzed, as well as their study habits, concentration, time management skills, and satisfaction with academic achievements, also their confidence in their ability to learn and remember at the time of examination. It is known that many students that enter the university, cannot meet the new challenges of better organization of academic work, planning time and greater dedication to study, which entails a higher risk of school failure. We must mention the importance of family problems in the school’s students, as an open and fluid communication between parents and the student can help as a protective effect and positively influence their psychological well-being and adjustment to the school. A harsh family environment is linked to the development of depressive symptoms and poor academic performance. These factors together could explain the results and behavior of the students with abnormal results which were detected in the study.

Conclusions

Of the scales studied in our CAS test, depression, academic problems, substance abuse and suicidal ideation were associated with statistically greater failure rates in the studied student population. This shows that there is an increased risk of low academic performance if the student has one or more of these four altered scales. The Draw a Person test had no correlation with school failure. The application, review and analysis of such standardized tests enable us to get to know the new student population better, detecting risk factors for poor school performance, and implementing strategies to strengthen personal ties, and academic and psychological support, to facilitate their adaptation to the college and improve academic performance.
Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Funding

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Conflicts of interest

The authors have no conflicts of interest to declare.

References

ORIGINAL ARTICLE

Antibiotic self-medication in university students from Trujillo, Peru

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KEYWORDS
Self-medication; Anti-bacterial agents; Bacterial drug resistance; Universities; Cross-sectional studies; Peru

Abstract
Introduction: Antibiotic self-medication is a kind of indiscriminate use of antibiotics. This practice has been growing worldwide, and has been identified as a risk factor for bacterial resistance (according to the WHO, it is one of the most difficult public health problems to combat in the XXI century). This activity has also been observed in the university population, and there is some literature reporting factors among young people that could increase it.
Objectives: To describe risk factors associated with antibiotic self-medication among university students from Trujillo, Peru.
Materials and methods: An observational, analytical, retrospective study was performed using a questionnaire. It was applied to 1000 college students selected by proportional allocation from three universities in Trujillo.
Results: Seventy percent self-medicated two or more times during the last year. The drug most often used for self-medication was amoxicillin, by 133 students (20.33%). An association was found between antibiotic self-medication and the female gender. No association was found between antibiotic self-medication and age (p = 0.46), economic monthly income (p = 0.83), knowledge level (p = 0.23), health sciences programs (p = 0.14) and college year (p = 0.15).
Conclusions: A high use of antibiotic self-medication was reported and a probable link to females. However, we could not establish an association between antibiotic self-medication and age, income, prior knowledge about antibiotics, school programs or college years.
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Introduction

Antibiotics are one of the most commonly purchased drugs worldwide, especially in developing countries, where the prevalence of infectious diseases increases their use.1 They represent a large impact due to the costs they generate,
the damage to health (adverse reactions and therapeutic failure), and poor therapeutic practices, such as long-term self-medication. These present a global public health problem.\textsuperscript{2,3}

Self-medication is the use of medications to treat common health problems without being prescribed by a doctor.\textsuperscript{4} However, self-medication in the case of the use of antibiotics has become a dangerous trend, which begins at an early age (adolescence). Studies reveal that this practice is facilitated by easy access to antibiotics, low knowledge about antibiotics, low income, the cost of medical consultation, and prior use of antibiotics, among others.\textsuperscript{5-8}

On the other hand, antibiotic self-medication (ABSM) can alleviate some symptoms, which leads some to stop attending medical advice. However, it has been shown to have negative consequences, such as treatment failure and adverse drug effects (leading to death in the most severe cases), but mainly increased bacterial resistance.\textsuperscript{9-11}

Bacterial resistance is considered a global public health problem, and is caused by the indiscriminate use of antibiotics, as seen in ABSM.\textsuperscript{12,13} The prevalence of this activity is greater in developing countries, in most cases due to a lack of regulatory systems worldwide, and reports indicate that self-medication is more prevalent in cities of low and middle income.\textsuperscript{3,14} In addition, other factors have been identified in developing countries, such as foreknowledge of antibiotics, age, and monthly income, among others.\textsuperscript{7,5} Another study reveals that this population tends to go to pharmacies, and their choice is mainly based on the recommendation of the pharmacist, as found in a Brazilian study, which concluded that 74\% of the pharmacies in a municipality sold antibiotics without a prescription.\textsuperscript{16}

ABSM rates are, on average, 50\% in Africa, 40\% in the Middle East, from 4\% to 75\% in Asia and 29\% in South America, compared to developed countries in Europe, with an average of from 3 to 19\%. Studies in China revealed rates of self-medication with antimicrobials from parents to their children to be 62\%.\textsuperscript{17}

The reasons for this high prevalence are multifactorial.\textsuperscript{18} The liberal practice of undergraduates to self-medicate with antibiotics is common, and students base their use on previous successful experiences. However, we have identified that there is low awareness of antibiotic use and students often misuse them.\textsuperscript{19}

In order to take action and prevent increased ABSM, which brings negative effects in the medium and long term, it was considered necessary to seek the prevalence of this activity in the university population of a city in Peru and to identify the main risk factors which could increase this prevalence.

Materials and methods

Population and study design

An analytical study using a cross-sectional survey of 1000 undergraduates from three universities in Trujillo was conducted, taking into account the population reference amount used in previous studies.\textsuperscript{7,12,19} Among the four most representative universities of Trujillo, The National University of Trujillo (UNT by its Spanish acronym) was selected as the only public university in La Libertad, along with 2 randomly selected private universities [The Private Antenor Orrego University (UPAO by its Spanish acronym) and The Northern Private University (UPN)]. The number of students used in the study was selected by proportional allocation based on the number of students enrolled in the 3 universities as per the university national census (INEI 2010) (http://censos.inei.gob.pe/cenaun/redatam_iniei/) (see Table 1).

Study questionnaire

A bibliographical review of previous studies was performed to identify the elements that form part of the survey instrument. Based on this, and taking into account questionnaires previously validated in other countries adapted to the local population of each country, we developed a questionnaire of our own.\textsuperscript{9,12} Then, a pilot with a group of 30 college students consistent with the study population was performed to establish changes in the content, design, reading comprehension or facility if needed. However, accurate data were obtained.

The questionnaire consisted of four sections, and contains open and closed questions. The first section recorded the socio-demographic characteristics of respondents such as age, sex, year of study, and economic monthly income. The second section consisted of nine closed questions to provide information on the practice of using antibiotics. The third section consisted of 13 questions to assess the respondents’ knowledge of antibiotics in three aspects: action and use (6 statements), side effects (3 statements) and antibiotic resistance (4 statements). The five-point Likert scale (1 = strongly disagree, 5 = strongly agree) was used to assess the participants’ responses.

Statistical analysis

The data obtained was entered into the Statistical Package for Social Sciences (SPSS version 23.0) for processing. The results are reported as percentages (95\% confidence interval). The Chi Square test ($\chi^2$) was used to establish significant difference. Associations were considered significant if $p < 0.05$.

Respondents that answered “strongly agree” or “agree” were classified as “agree”, and those who answered “strongly disagree” or “disagree” were classified as

\begin{table}[h]
\centering
\caption{Sample size by proportional allocation.}
\begin{tabular}{|l|c|c|c|}
\hline
University & Population & Percentage & Sample \\
\hline
(N = 33,696) & (N = 1000) & \\
\hline
National University of Trujillo & 16,741 & 49.70\% & 497 \\
Antenor Orrego Private University & 9263 & 27.50\% & 275 \\
Northern Private University & 7692 & 22.80\% & 228 \\
\hline
\end{tabular}
\end{table}
“disagree”. A scoring system was applied to measure knowledge. One point was awarded for the correct answer (strongly agree or agree with the correct statement and strongly disagree or disagree with the incorrect statement), and zero for each incorrect or uncertain response, with a maximum obtainable score of 13 for each respondent. The score classified the knowledge into three levels: low (0–6), moderate (7–10), and high (11–13).

**Ethical considerations**

This research was carried out respecting the ethical and moral guidelines governing biomedical research in the latest update of the Declaration of Helsinki, General Health Law No. 26842, Articles 25 - literal c and 53, and according to the Code of Ethics of the Medical College in Chapter 6 Article 42.

We report that only the researcher personal will have access to this data, and the verbal consent of each of the respondents was obtained before applying the questionnaire.

**Results**

A total of 1000 undergraduate students from 3 universities in Trujillo were included in this study. The average age of all respondents was 19.82 years. Women accounted for 49.2% of the sample studied.

Six out of ten university students said they had consumed at least one antibiotic in the last 12 months preceding the survey. Of these, 70% consumed 2 or more antibiotics in the last year (see Table 2).

Sixty three percent of college students who self-medicate took the recommendation of a pharmacist as the basis of their choice of antibiotic. Half of the population who self-medicated with antibiotics decided to stop taking them after the disappearance of symptoms (see Table 2).

The antibiotic most commonly used for self-medication was amoxicillin, by 133 university students (20.33%). Sore throat and fever were the most common complaints, with 54.1% and 47% respectively of students who decided to self-medicate with antibiotics. Approximately one third (35.32%) reported using symptomatic drugs such as paracetamol.

The study shows that 57.3% of college students have a low level of knowledge about antibiotics (see Table 2).

We studied the association between ABSM and certain factors, such as gender, age, monthly income, year of study, a career related to health sciences, and knowledge level. We found an association between the female gender and ABSM (OR: 1595; 95% (1226–2076)). By contrast, no association between ABSM was found with age, monthly income, level of knowledge, careers related to health sciences or year of study (see Table 3).

**Discussion**

This study is the first conducted in Peru to demonstrate ABSM prevalence and factors associated with this activity in college students.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Characteristics of respondents (N=1000).</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Frequency</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>492</td>
</tr>
<tr>
<td>Male</td>
<td>508</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
</tr>
<tr>
<td>15–17</td>
<td>386</td>
</tr>
<tr>
<td>18–21</td>
<td>385</td>
</tr>
<tr>
<td>21–25</td>
<td>177</td>
</tr>
<tr>
<td>25–30</td>
<td>41</td>
</tr>
<tr>
<td>30 or more</td>
<td>11</td>
</tr>
<tr>
<td><strong>Economic income</strong></td>
<td></td>
</tr>
<tr>
<td>&lt;750.00 per week</td>
<td>321</td>
</tr>
<tr>
<td>From 750.00/w to 1500.00/w</td>
<td>322</td>
</tr>
<tr>
<td>From 1501.00/w to 3000.00/w</td>
<td>178</td>
</tr>
<tr>
<td>&gt;3000.00/w</td>
<td>179</td>
</tr>
<tr>
<td><strong>Career studies</strong></td>
<td></td>
</tr>
<tr>
<td>Nursing</td>
<td>15</td>
</tr>
<tr>
<td>Stomatology</td>
<td>8</td>
</tr>
<tr>
<td>Pharmacy and Biochemistry</td>
<td></td>
</tr>
<tr>
<td>Human Medicine</td>
<td>113</td>
</tr>
<tr>
<td>Obstetrics</td>
<td>3</td>
</tr>
<tr>
<td>Psychology</td>
<td>12</td>
</tr>
<tr>
<td>Other</td>
<td>806</td>
</tr>
<tr>
<td><strong>Self-medication with antibiotics</strong></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>654</td>
</tr>
<tr>
<td>No</td>
<td>346</td>
</tr>
<tr>
<td><strong>No. of times</strong></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>195</td>
</tr>
<tr>
<td>2 or 3</td>
<td>325</td>
</tr>
<tr>
<td>4 or more</td>
<td>134</td>
</tr>
<tr>
<td><strong>Antibiotic recommendation</strong></td>
<td></td>
</tr>
<tr>
<td>Pharmacist</td>
<td>413</td>
</tr>
<tr>
<td>Family opinion</td>
<td>278</td>
</tr>
<tr>
<td>Previous prescription</td>
<td>210</td>
</tr>
<tr>
<td>Own experience</td>
<td>158</td>
</tr>
<tr>
<td>Commercial</td>
<td>40</td>
</tr>
<tr>
<td>Other</td>
<td>49</td>
</tr>
<tr>
<td><strong>Most used antibiotic</strong></td>
<td></td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>133</td>
</tr>
<tr>
<td>Other penicillins</td>
<td>19</td>
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<tr>
<td>Cephalosporins</td>
<td>7</td>
</tr>
<tr>
<td>Macrolides</td>
<td>36</td>
</tr>
<tr>
<td>Quinolones</td>
<td>4</td>
</tr>
</tbody>
</table>

High rates of antibiotics without a prescription were identified in our study: 65.4% (654/1000). These results are similar to previous studies in Ghana and Uganda (with rates of 70 and 75%, respectively), but higher than in China, European countries and Brazil (38–48%, 40% and 29.3%, respectively). This high prevalence could be...
Table 3 Association between antibiotic self-medication and gender, age group, monthly income, university degree and level of knowledge.

<table>
<thead>
<tr>
<th>Characteristics of respondents</th>
<th>Antibiotic self-medication</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>306</td>
<td>202</td>
</tr>
<tr>
<td>Female</td>
<td>348</td>
<td>114</td>
</tr>
<tr>
<td>Age group (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15–17</td>
<td>260</td>
<td>126</td>
</tr>
<tr>
<td>18–21</td>
<td>247</td>
<td>138</td>
</tr>
<tr>
<td>21–25</td>
<td>118</td>
<td>59</td>
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due to the difficulty of access to the Health Care System and insufficient income levels to access private physicians. The similarity with studies in Ghana and Uganda is possibly the result of the sociodemographic characteristics of the populations studied, and belonging to developing countries, which does not happen with countries like China, Brazil and European countries.

In our study, we found that 40% of college students attended a pharmacist directly and 30% used prior medical prescriptions for similar symptoms. This correlates with the studies found in the literature which show that the patient’s expectation is a factor in antibiotic prescriptions by pharmacists. 10,22

The most common drug used by college students who self-medicated was amoxicillin, by 133 (20.3%), which is also consistent with other published studies. 23,24 This may be because it is the most used antibiotic worldwide and the antibiotic most prescribed by doctors.

Our study found an association between ABSM and the female gender, as found in a study conducted in the UK. 25 No association between ABSM and age group, monthly income, year of university study, study program or level of knowledge was found, as is seen in other studies, which may be because the number of respondents in each subgroup were insufficient to establish an association. 14,25,26

It must be mentioned that in Peru, the General Health Law 26842, in Article 26, states that: “Only doctors can prescribe medication. Dentists and obstetricians may prescribe within the area of their competence.” Article 33 states: “The pharmaceutical chemist is responsible for dispensing, user information and guidance on the use of medicines. They are not authorized to prescribe drugs.” However, the results of our study show that an audit system should be implemented for pharmaceutical centers, so that they are susceptible to the corresponding fine prescribed in the Pharmaceutical Establishments Regulation (RM-Ministerial Resolution No. 304-2002/SA/DM). This would help reduce the irrational use of antibiotics in our population, also, the data revealed will form the basis for future campaigns on the rational use of antibiotics in this population group.

Being that this analytical cross-sectional study used a survey to estimate the prevalence of ABSM in the past, recall bias cannot be ruled out. Respondents could also have no knowledge about what an antibiotic is, although this may be a minor problem, particularly among our respondents, as they were all college students. For these reasons, it is unclear whether our findings are generalizable to other universities in Peru.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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Conflicts of interest

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LETTER TO THE EDITOR

Multidisciplinary College Camp for Services and Research (CUMIS) in Colombia: Experience and perspectives

Dear Editor,

Sufficient data exists to support community interventions and research activities as a fundamental part of the integral formation of medical students. Recently, the medical students’ associations worldwide have begun to integrate research and social work in interventions on target populations. In Latin American countries such as Peru, Colombia, Bolivia, Panama, Paraguay and Venezuela, this kind of work has been promoted by Scientific Medical Student Societies from different universities related to the health sciences and based on four main areas: education, social projection, research and health care.  

In the specific case of Colombia, the country’s major medical association, the Colombian Medical Student Association of Scientific Societies (ASCEMCOL) in its 27 years of experience has integrated students from 33 medicine faculties in activities of a scientific and social character. Since 2010, the Multidisciplinary College Camp for Services and Research (CUMIS) has been conducted annually, with successful previous results in 6 different rural communities of Colombia. This year, the experience has been led by the Scientific Association of Medical Students of Risaralda (ACEMRIS), belonging to ASCEMCOL, with the support of the Latin American Federation of Medical Students’ Associations (FELSOCEM), in the municipalities of Santa Cecilia and Pueblo Rico in the Department of Risaralda, from the 2nd to the 6th of July.  

Risaralda is located in the west central area of Colombia and has 14 municipalities. Pueblo Rico has a population of over 12,000 inhabitants, of whom 9658 live in the rural area. Santa Cecilia has a population of about 3000 inhabitants and approximately 60% of these have no education. Both municipalities are in the settlement of the Emberá-Chamí indigenous community. Although Risaralda has similar or better demographic indicators than the national average, Pueblo Rico and Santa Cecilia are the exception, with high unsatisfied basic needs and mortality rate indexes. There is a low life expectancy, even lower than the Choco Department, which is the least developed zone of Colombia. Due to this, the precarious situation in which they live is reflected in the low quality of life and a large number of infectious diseases, such as malaria, leishmaniasis and tuberculosis.

A total of 300 people participated in the event: 16 health care professionals, 20 medical students from the organizing committee and 264 medical student members of ASCEMCOL and FELSOCEM. Attendees were divided into 15 teams, each one with a health care professional in charge of a group of 17 students, who were divided into extramural teams (rural villages) and local teams (municipalities). Medical interventions were conducted in rural and urban zones, drugs were delivered according to the patients’ clinical diagnoses, and education campaigns were performed regarding hygiene, lifestyles, sexual health, promotion and prevention issues.

Our experience demonstrates again, that these events are beneficial for disadvantaged communities, and also for the medical students involved, who have had the opportunity to develop competencies and skills in: public health, primary health care, research, doctor-patient relationships and teamwork. Clearly, more interventions such as the CUMIS are needed in our country, especially in the less developed areas. For that reason, the medical students belonging to ASCEMCOL are determined to make a bigger positive impact on public health in neglected communities every year.

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References


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Impact of air pollution in respiratory allergic diseases

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Abstract Allergic respiratory disease, which includes allergic rhinoconjunctivitis and asthma, is one of the most common diseases, with a major impact on a patient’s quality of life. Air pollution is one of the main factors associated with the development of allergic respiratory disease, it has been shown to impair lung development in children and adolescents. The origins of particulate matter produced from various sources, including those issued by traffic and the burning of fuels such as coal, gasoline and diesel. Diesel emissions represent the majority of the particulate matter in urban air pollution. It has been found that the co-exposure of diesel emissions and airborne allergens increases allergen-specific IgE levels, severity of asthma, inflammation and airway hyper-responsiveness. In vivo and in vitro studies have reported the activation of anti-transcription and pro-inflammatory mediators. Polycyclic aromatic hydrocarbons, metal components or metabolites may increase due to the formation of oxygen reactive species that interact with DNA, producing different types of damage as oxidative damage.

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Introduction

Allergic respiratory disease (ARD) is a frequent atopic condition, manifesting through allergic rhinoconjunctivitis and asthma. Affecting up to 40% of the population worldwide and with a significant impact over the quality of life of those who suffer from it.1,2 In recent years there has been a considerable increase of air pollutants due to the development of large cities with high industrial activity and linked to an ever increasing number of cars; thus becoming an emergent problem in many countries.3 In the US, the cost of asthma attributable to ozone and nitrogen dioxide exposure is 441 million dollars a year, 202 million dollars a year in Los Angeles alone.4 In a different American study, estimations suggest a cost of 18 million dollars a year in health services directly

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E-mail address: aarias45@hotmail.com (A. Arias-Cruz).
or indirectly attributable to asthma crises linked to exposure to traffic-derivative pollutants.  

The development of an allergic disease takes place due to the interaction of genetic predisposition and environmental determinants. Air pollution is one of the main environmental factors linked to the onset of ARD, as well as its exacerbations. Air pollution has been proven to alter the pulmonary development of children and teenagers.  

Air pollution

Air pollution is defined as the alteration of the pureness and quality of air caused by the emission of chemical or biological substances released naturally or produced by man and his everyday activities. Among these are particulate matter (PM) with a diameter of less than 10 μm (PM 10), inhalable fine particulates if their diameter is less than 2.5 μm (PM2.5) and ultrafine particulates (UFPS) which are smaller than 0.1 μm. According to the World Health Organization (WHO), PM2.5 is 25 μm/m3, and the daily allowed exposure limit for PM10 is 50 μm/m3. As reported, every increase of 10 mg/m3 of PM10 was linked to an 0.46% increase in the mortality rate in the US. In Mexico, the Official Mexican Standard (NOM) by its Spanish acronym) NOM-025-SSA1-2014 establishes the permissible limit values for concentrations of PM10 and PM2.5 suspended particles in the environment, which are, for particles under 10 micrometers (PM10) and 2.5 micrometers (PM2.5), an average limit of 24 h of 75 μm/m3 and 45 μm/m3 respectively.  

PMs are produced from several sources, including those emitted by traffic, carbon combustion, gas, diesel and other types of fuels. Secondary emissions from diesel represent the majority of particulate matter from urban air pollution. The size of the particle, its surface and its chemical composition determines the risk that it represents in a patient who is exposed to it regularly. According to their size, the MPs can easily access the airway, even reaching the alveoli and thereby causing direct damage as a result of irritation, or provoking oxidative stress by activating various signal transmission pathways and transcription factors.  

In 2008, Glueckman et al. showed that prenatal and postnatal exposure to air pollution negatively influences developmental plasticity, resulting in a wide range of diseases in childhood. Recently, Fleisch et al., proved that exposure to contaminated air during pregnancy is associated with an increased risk of adverse birth outcomes. However, the negative impact of air pollution goes further. Deng et al. found a significant association between the development of asthma and allergic rhinitis in Chinese children whose mothers were exposed to air pollution during pregnancy. All these findings could be explained by different epigenetic mechanisms, such as DNA methylation, where the different contaminants play an important role in the development of allergic diseases.  

Ozone (O3) is a molecule composed of 3 oxygen atoms. It is formed from the dissociation of an oxygen molecule (O2) by joining a released atom to an O2 molecule. Tropospheric ozone is a colorless gas created by photochemical reactions between nitrogen oxide and volatile organic compounds from the combustion of gasoline, diesel or fossil fuels. It acts as a strong oxidant that has been associated with persistent structural damage and injury to lung tissue, which leads to exacerbation of asthma symptoms. Further epidemiological studies are needed to know and document the morbidity and mortality rates associated with ozone exposure.  

Traffic smoke has been shown to have an association with accelerated growth of allergies and asthma in childhood. This process involves the residue oil fly ash (ROFA), which is a complex mixture of sulfates and metals, specifically vanadium, that have the potential ability to influence immunity and cause damage to various systems, being a critical factor in the hyper-responsiveness and injury of the airway.  

Air pollution and aerospheric allergies

Air pollutants have the ability to modify the allergenicity of certain pollens. They facilitate dispersion of the pollen allergen into smaller fractions. Specifically ozone, in an experimental model, produced a structural change in the coating layers of the pollen, inducing modification in pollen-plant interactions, pollen-human cells and potentiating the allergenic properties of pollen.  

Kim et al. reported that exposure to ozone was significantly associated with the rate of new sensitization to outdoor allergens, which could explain the mechanism for the increase in the prevalence of allergic rhinitis. Likewise, it has been found that the co-exposure to diesel and airborne allergens emissions increases the levels of allergen-specific IgE, asthma severity, and airway inflammation and hyperreactivity.  

Air pollution and ARD

According to the World Health Organization (WHO), several million people around the world suffer from rhinitis, and an estimated 300 million have asthma, and these diseases significantly affect the patient’s quality of life and family environment, leading to a negative impact on the socioeconomic well-being of society. The major problem of environmental pollution in industrialized countries is responsible for nearly 2 million deaths per year in developing countries.  

Air pollutants have the ability to affect the presentation of asthma in different ways: acting as a stimulator or trigger, aggravating pre-existing airway inflammation, and modifying the response to aeroallergens or substances that act as irritants in the airways.  

The way in which air pollutants impact the development of asthma and allergies has been the subject of investigation and controversy. Two studies in California found that contaminants related to vehicular traffic can cause asthma in older children. Another study reported that children exercising in areas with high concentrations of ozone were more likely to develop asthma. A Japanese study looked for an association between asthma and nitrogen oxide (NO2) levels, with a sample universe of 2506 children studied over a period of 4 years, and concluded that children living at a distance of less than 50 m from roads with heavy vehicle loads were more prone to asthma development.  

There is a “modern” indicator of pollution, NO2, which has been attributed to an increase in the presentation of
asthma and wheezing. However, in another study, the agent was unrelated to the prevalence of allergic symptoms. What was demonstrated was the increased risk of recent symptoms of both allergic rhinitis and asthma in schoolchildren associated with SO₂ and CO levels. Diesel engine particles (DEP), the main constituents of urban air pollutants, have been shown to be able to modulate the pulmonary immune response by stimulating the function of dendritic cells and thus induce inflammatory processes in the airway. Diesel emissions contain small particles of various sizes, ranging from nanoparticles to coarser particles, the latter of which are the most easily drawn into the lungs and can be kept suspended in the atmosphere for long periods of time. These consist of a carbonaceous core with a large surface area to which other chemicals are adhered, such as polycyclic aromatic hydrocarbons (PAHs) as well as heterocyclic, aldehydes and aliphatic hydrocarbons. These diesel particles are able to reach the cell’s surface and activate molecular mechanisms by stimulating human airway epithelial cells to produce cytokines, which lead to inflammation. In in vitro studies, once these particles reach the epithelial cells, IL-8, macrophages, granulocyte colony stimulating factor, T cells and intracellular adhesion molecules (ICAMs) are released, which are found in significantly higher amounts in patients with asthma. It has also been shown to affect gene expression by inducing eotaxin from epithelial cells.

Salvi et al., studied the effects of high-level diesel inhalation in a chamber; a significant increase in inflammatory cells (neutrophils, B lymphocytes, mast cells, CD4 and CD8 lymphocytes) was demonstrated, along with the positive regulation of ICAM. Reactive oxygen species, due to the effects of DEP and their consequent release of IL-8, ICAM-1, GM-CSF and RANTES, are inhibited on exposure to antioxidant agents such as N-acetylcysteine.

The mechanisms which cause double chain DNA break in pulmonary cells have been found to be secondary to the impact of air pollution in the mRNA expression in humans due to the activity of the telomerase and phosphorylation of H2AX histone. DNA damage induced by particulate matter made of metals (copper, iron, nickel, vanadium, zinc and lead) and polycyclic aromatic hydrocarbons (PAHs) is metabolized and then covalently bonded in the DNA. The components of the metals or the metabolites of PAHs can be increased in the formation of oxygen reactive species that interact with the DNA, producing damage of different types, such as oxidative damage.

Variations in environmental influences on individual genotypes can lead to heterogeneous endotypes of asthma. Several phenotypes of severe clinical expression may overlap in one patient, and the same clinical phenotype may result in different endotypes, which would be reflected in the severity of the disease and its response to conventional treatments.

Intramural contaminants

Today, a large number of people from industrialized cities spend most of their time at either their home or their job. It has been reported that more than half of the air inhaled during one’s life comes from an intramural environment. The sources of intramural contaminants come mainly from cigarette smoke, combustion products such as candles or incense, and volatile organic compounds emitted by building materials, paints, furniture with sponge cushions and products containing polyvinyl chloride (PVC). In a study of newborns in Germany, the concentrations of intramural contaminants (PM₁, PM₂.₅ and PM₁₀) were higher than the PM₁₀ extramural values recommended by the European Union.

Choi et al. found that the average concentration of individual compounds of volatile organic compounds was consistently higher in the households of children diagnosed with asthma, rhinitis, and eczema compared to the homes of children in a control group. These results suggest that intramural air exacerbates and/or induces the multiple symptoms of allergy, asthma, rhinitis and eczema.

Conclusions

Air pollution is a key factor in the development and increase of ARD exacerbations. The epigenetic, cellular and molecular mechanisms that directly or indirectly intervene in allergic diseases, and how they contribute to the negative impact of patients’ quality of life have not yet been extensively described. Patients are advised to minimize prolonged exposure to pollutants by methods such as reducing extramural activities on days with high levels of air pollution and promoting reforestation of non-allergic trees in urban areas. As health personnel, we have the obligation to unite our efforts, participate actively in forums and support national and international environmental policies with the purpose of reducing the impact and consequences of this health problem in the future.

Conflict of interest

The authors have no conflicts of interest to declare.

References

Acute leukemia (AL) is the most common malignant disease in children, and one of the most important causes of death in pediatric age. For practical purposes, one in three children with cancer has AL, and three to four new cases occur each year per 100,000 children under 15 years of age. In Mexico, there are about 1000 new cases diagnosed per year, so the pediatrician and family physician ideally need tools that allow for early diagnosis.¹

There are a series of important prognostic factors, particularly in acute lymphoblastic leukemia (ALL), which is the variety that explains 85–90% of all cases of leukemia in children. This factors allow us to make a distinction between at least three risk groups for relapse of the disease, namely, low risk, standard risk and high risk. Each of these three groups receives different chemotherapy treatment protocols; children at high risk receive the most intense treatment and those at low risk are in turn easier to handle and less likely to generate complications.²

It is clear, that to offer the most appropriate treatment for each of the children, it is essential to carry out this distinction of risk groups and prevent a patient at low risk of relapse from receiving an intense treatment that exposes them to unnecessary toxic effects, and also preventing a high risk patient from receiving an insufficient chemotherapy scheme, which would significantly reduce their chances of being cured. It should be stressed that these prognostic factors are not life-or-death sentences, just elements that allow us to offer the best possible treatment for each patient.

These risk factors can be divided into three groups: those having to do with the characteristics of neoplastic cells, those having to do with treatment response and those having to do with the characteristics of each patient. A very important example regarding neoplastic cells is referred to as the presence of the Philadelphia chromosome (Ph+). If a child with this condition receives a standard treatment, the chances of being cured are almost 0%, while a treatment that includes tyrosine kinase inhibiting drugs, such as imatinib, significantly increase the chances of a cure.

Regarding treatment response, as with virtually any disease, patients who respond well to chemotherapy protocols are more likely to be cured. This response assessment can be carried out in different ways. One of the most commonly used assessments around the world was proposed by a German group almost 20 years ago. In it, children with ALL initially receive 7 days of treatment solely with corticosteroids. If at the end of this week the patient has less than 1000 blast cells per mm³ in their peripheral blood it is considered a favorable response and these children’s chances of being cured are set higher. If, on the contrary, the patient’s leukemic cells are not reduced below this figure, it will be necessary to administer more intense treatment protocols. Fortunately these cases are less frequent in most populations.

Other institutions perform bone marrow studies, fifteen days after starting treatment. And finally, any location that has one, usually performs a determination of minimal residual disease (MRD) at the end of the first month of treatment.

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which has been our center's policy for the last eight years. With an MRD, and with the use of monoclonal antibodies, we can quantify the number of neoplastic cells the patient has at the end of the first month of treatment with certainty. In this manner, we can objectively evaluate 500,000 or more cells and determine if the patient has <0.1 × 10^6 leukemic cells per mm^3, which is to say, less than 1 malignant cell for every 10,000 evaluated. When the MRD is negative, the possibility of being cured increases, otherwise, the patient should be treated with more intense chemotherapy protocols and even consider a hematopoietic progenitor cell transplant. Previously, the patient would be evaluated after one month of treatment to see if he had achieved complete remission (less than 5% blasts in the bone marrow study) by a morphological review conducted by the hematologist after observing between 500 and 1000 cells by microscope. This was an "operator dependent" method and was therefore less accurate.

The pediatrician and primary care physicians do not have any participation in the workup mentioned above, i.e., the cytogenetic characteristics or immunophenotype markers are beyond the reach of many of us, and response to treatment protocol that is used depends mainly on the hematologist. In addition, they cannot influence the prognostic factors that depend on patient characteristics, such as gender (the prognosis is slightly better in women), race (the Anglo-Saxon population shows better results than blacks or Hispanics, which is determined, among other factors, by specific genetic alterations) and age at diagnosis (children between one and nine years old have the best outlook).

The early suspicion of a diagnosis is the only prognostic factor that a pediatrician or primary care physician can influence, and therefore has an influence on the absolute leukocyte number in the initial blood count (BH) being less than 50,000/μL, most medical groups accept that children diagnosed with less than this figure have a better prognosis than those with higher counts, which are associated with an increased risk of relapse and should receive more intense chemotherapy schemes.

What happens when a child is diagnosed with more than 50,000 white blood cells per microlitre? Initially, they will be included in the group of patients receiving more intensive treatment, which is usually more toxic and more likely to develop complications, with an increased risk of presenting infiltration to the central nervous system and also in developing serious complications in the early days of treatment, such as tumor lysis syndrome. In effect, the fact of having more than 50,000 white blood cells per microlitre at diagnosis is associated with a smaller possibility of a cure.

In children with less than 50,000 leukocytes at diagnosis and without other adverse prognostic factors, a cure rate of up to 80% can be achieved. In a group of patients with more than 50,000 leukocytes at diagnosis, the chances of being cured would be reduced to 50%. It is important to note that many times the course of the disease is so fast that, however early it is suspected and the necessary workup measures carried out, a patient with ALL can present with very high leukocyte counts from the beginning.

Most of the time, the diagnosis of ALL revolves around the complete blood count (CBC), because of the clinical situations which result in requesting them, as well as the significant interpretation data that can be derived from it.³

The following are the instructions for requesting a CBC in children.

**Anemic syndrome**

The vast majority of patients with anemic syndrome (fatigue, weakness, paleness, hyporexia, headache, etc.) will have a different diagnosis than leukemia. In fact, the diagnosis will be iron deficiency anemia over 90% of the time. However a CBC should still be requested. It is important to mention that to continue considering a diagnosis of iron deficiency anemia, the anemia should be microcytic and hypochromic, with high RDW, and normal to elevated leukocytes, and platelets. In fact, if in addition to the above, the patient shows a low percentage of reticulocytes (which are rarely requested), the diagnosis of iron deficiency anemia has a high degree of certainty without the need for any other test.

**Purpuric syndrome**

A child with mucosal bleeding and manifested petechiae, ecchymosis, or epistaxis, requires a CBC. In these cases, most patients will have an immune thrombocytopenic purpura. It is important to note that these patients are basically "healthy" children who only have purpuric syndrome and a low platelet count in the CBC. Everything else is normal, the child has no fever, no weight loss, and no hyporexia, adenopathy, splenomegaly or bone pain.

**Bone pain**

One in four children with ALL manifest bone pain. It should be mentioned that the most common cause of pain in children are growing pains. An 80% of children with growing pains refer them in the lower limbs, and as being symmetrical, very intense, lasting a short time and, most importantly, recurring weeks or even months later. So with any other type of bone pain in children, ALL should be considered and a CBC should be requested.

**Splenomegaly**

All children with a palpable spleen should get a CBC, without exception. Among the most common causes for splenomegaly in children are viral infections. Regardless of how it is discovered, once splenomegaly is noted, a CBC should be performed and the diagnosis of ALL should be excluded.

**Fever**

Considering the large number of children who have a fever, when would the fever call for doing a CBC? If the patient has three or more days of fever without clinical improvement; or has several febrile episodes in a short period of time, or if along with fever, the patient shows any of the aforementioned conditions (anemic or purpuric syndrome, bone pain and splenomegaly), then he should receive a CBC.
It should be made clear that to request a CBC in any of the situations mentioned above does not mean that the child has ALL. Requesting a CBC simply allows us to make a timely diagnosis. Regarding the proper interpretation of the CBC, it should consider a number of very important data. For example, four out of five patients with acute leukemia have anemia, which is normocytic and normochromic, so the diagnosis should not be excluded just because the patient does not have anemia. Also, one in five children with ALL has no thrombocytopenia in the same way that occurs with anemia, so having a normal platelet count does not exclude the diagnosis.

Pancytopenia is defined as, upon performing a CBC, having a diminished hemoglobin, platelets and leukocyte count. That is, affecting all three cell lines simultaneously, and this must be considered a medical emergency, which is to say that the patient must be evaluated with the intention of confirming a diagnosis as quickly as possible, as the majority of children with pancytopenia also have ALL.

It is not difficult to diagnose leukemia or suspect it with a CBC reporting more than 50,000 leukocytes. However, it is very important to consider that 50% of children with ALL present with less than 11,000 leukocytes on an initial CBC, so it should be clear that there can be any white blood cell count in the initial CBC; only 20% of patients have more than 100,000 leukocytes at diagnosis and less than 7% have more than 200,000 per microliter.

Another consideration is related to the common fact that the presence of blasts or immature cells in the leukocyte differential is not reported in the initial CBC; for practical purposes, all cases of ALL are present in the peripheral blood at diagnosis. The reasons they are not reported are, among others, a lack of experience on the part of the smear's observer, a lack of certainty in reporting them, and the presence of a reduced number of them, especially in cases with low leukocyte counts. It is also important to note that blasts are very often reported as atypical lymphocytes, and appear to be handled as synonyms despite their different origins. It is also common for reports to include terms such as "immature", "ugly" or "suspicious", leading to the aforementioned fact that even though no blasts are reported in the CBC, the diagnosis of ALL should not be discarded.

Most of the time, the diagnosis of ALL is not very complicated for hematologists, because they can count on the use of bone marrow aspirates for suspected cases. The problem is that patients must come to the clinic for that study. Another important factor is the lack of communication between the doctor and the laboratory personnel; the staff is usually more interested in a case in which the doctor tells them about suspected acute leukemia.

Finally, we must re-emphasize the following data (Table 1):

<table>
<thead>
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<th>Table 1 CBC requests and findings.</th>
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<td>A CBC should always be requested in cases of</td>
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<td>Anemic syndrome</td>
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<tr>
<td>Purpuric syndrome</td>
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<tr>
<td>Splenomegaly</td>
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</table>

*Request a CBC in all cases of children with anemic syndrome, purpuric syndrome and splenomegaly. CBC should also be considered in children with bone pain that does not appear to be growth-related and in children with a fever that is long-standing and unresponsive to conventional treatments.

Pancytopenia should be considered a medical emergency. The leukocytes count in ALL can be low, normal or high. The absence of "blasts" or "immature cells" in the CBC report do not exclude a diagnosis of acute leukemia.

Carrying out a timely diagnosis for ALL results in a better prognosis, and considering what has been referred in this article, the appropriate involvement of the pediatrician or primary care physician is of great importance for the course and outcome of children with this disease.

Conflict of interest

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References

EXPERT’S CORNER: A PERSONAL APPROACH

Glucose tolerance test as a tool in the diagnosis of diabetes mellitus

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In everyday medical practice, it is essential to establish safe and reliable criteria for the diagnosis of diseases, so that when physicians encounter certain clinical circumstances, they are able to recognize the problem more easily and accurately, and thus provide the necessary therapeutic measures needed to solve the problem, or at least control it.

This applies for all diseases; however, the level of difficulty for the diagnosis of each pathology is different; some are relatively simple, while others are much more complicated. Take diabetes mellitus as an example of a pathology which represents different degrees of difficulty in establishing a diagnosis.

Diabetes mellitus is a chronic disease, one which has existed since the beginning of mankind. Today, many of the mysteries surrounding this disease have been explained through scientific research; moreover, the knowledge of this pathology has allowed medical science to more efficiently control most of the problems this pathology represents. However, despite how much we know about this disease, there are still many unanswered questions, and it continues to be highly prevalent amongst the general population, with increasing morbidity and mortality.

Recent publications, report that at the present, there are over 420 million people with diabetes mellitus. Calculations suggest that by the year 2025, if current incidence and prevalence tendencies remain unchanged, the percentages of the population with diabetes will be as follows; 7.6% in the US, 14.5% in Mexico, 10.5% in Colombia and 12.2% in Argentina, and so on, increasing worldwide.1

It is important to have tools which are simple yet safe. In other words, tools which have enough sensitivity to detect each and every one of the cases, and also have the proper specificity so that the disease is not under- or over-diagnosed.

Establishing a diabetes diagnosis is a task which ought to be faced by physicians from all specialties, since this disease does not respect age, gender, race or social class. Primary care physicians, as well as general practitioners, pediatricians, internists, surgeons and gynecologists, among others, may face a patient with diabetes. Therefore, it is important for them to know which diagnostic methods to use in order to accurately establish the diagnosis.

A large percentage of type-II diabetes cases do not represent significant difficulties, since the triad of polydipsia, polyuria and polyphagia is evident and quickly point the doctor in the direction of suspicion of diabetes.

However, a large percentage of patients are either asymptomatic, or the symptoms have not acquired enough intensity, and thus have not yet been detected by the patient.

This situation is different for type I diabetes, which occurs more frequently in children or young adults and where the previously mentioned symptoms are usually extremely evident and dramatic. And if there is not a timely diagnosis and the proper therapeutic measures are not taken, the metabolic alteration is quickly exacerbated and can lead to a circumstance of diabetic ketoacidosis in a...
very short period of time, sometimes in days, which remains a severe acute complication, and may even be fatal. In cases of type II diabetes with classic symptoms, or type I diabetes with dramatic symptoms, ensuring the diagnosis with laboratory tests is quite simple, since either one or two determinations of 200 mg % of glucose or higher in blood and the presence of glycosuria are enough to accurately prove a diagnosis. When in doubt, or when glycemic is not over 200 mg %, we may need to re-apply the glycemic test or complement it with other tests, such as glucose in blood 2 h after administering an oral load of 75 g of dextrose (it must be dextrose). Some laboratories give the patients sugar, which is sucrose, by mistake or ignorance. This can lead to false interpretations. In these cases, if post-loading glucose remains over 140 mg % and under 200 mg %, it means that we are treating a patient, which is intolerant to carbohydrates but has not yet developed diabetes, and should be treated accordingly. These patients require periodical monitoring; since, over an undefined period of time, they have high probabilities of developing the disease.

So, when does it become necessary to conduct a glucose tolerance test in order to establish a diagnosis? As mentioned above, we can ensure diagnosis with a high percentage of patients with type II diabetes and most patients with type I diabetes with only one glycosuria and a glycaemia. In fact, only a small percentage of cases require the full glucose tolerance test to be diagnosed.

Diabetes specialists, as well as endocrinologists, are probably the physicians, which order patients to undergo this method the least often. Why is that? There are several reasons: first, because in many cases the doubt fades after a thorough clinical history, where family background is researched, as well as the patient’s weight and waist circumference, and the presence of other morbidities which are commonly found in patients with diabetes, such as obesity, high blood pressure, dyslipidemias (mainly hypercholesterolemia or hypertriglyceridemia), hyperuricemia, or gout (multiparity for women). The presence of one or more of these conditions makes the patient highly suspect for diabetes, and in these cases, a simple glucose determination over a fasting period and/or glycosuria followed by periodical monitoring may be enough without the need to conduct a full glucose tolerance test.

On the other hand, we should mention that the test is long, uncomfortable and expensive; moreover, interpretive criteria have varied with time and are not always reliable. Also, nowadays, in order to be certain, it is convenient to include the simultaneous determination of insulin, which, while very useful data, since it determines the presence or absence of hyperinsulinemia, improving diagnostic certainty, makes the test much more expensive for the patient.

I am under the impression that the glucose tolerance test has been overused for many different reasons, due to a lack of experience, ignorance, or other reasons. Sometimes patients are just sent to the lab so that he or she feels that the best efforts are being made. Sometimes we observe that a patient who has already been diagnosed with diabetes mellitus, either in the past or recently, is sent to have the curve test performed. Nothing could be more absurd; the test is conducted to help make the diagnosis, if the diagnosis has already been made, the test is unnecessary. In any case, control tests ought to be used, such as glycosylated hemoglobin or self-monitoring.

In my personal opinion the test should be limited to very special cases and in general terms ought to be reserved for scientific research, with clear objectives and appropriate protocols. In medical practice, diagnosis can be made through simpler methods. Nevertheless, there are special cases, such as in obstetrics and gynecology, where this test is justified, or when there is doubt in the results of a routine post-load glucose test. This test is also usually conducted at 28 weeks of pregnancy, then if the result is abnormal, a full glucose tolerance test is necessary in order to clear up the situation and give the proper therapy if needed.

My personal advice noted above, of limiting full tests to very special cases and preferably to those patients within a study with complete and approved protocols, is not necessarily a reflection of what is accepted in worldwide published literature. There are still doubts and there are publications from different times and places by very prestigious authors such as those listed in the bibliography at the end of this article, authors who defend an opposing position regarding this point. For those who may be interested in this topic, we recommend these articles.2,3

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