

Exocrine pancreas function - sex, age, estrogenic and cholinergic tone - preliminary clinical value of citrates “magic powder”

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Summary

This study pivots on exocrine pancreatic secretion. We choose 45 years limit, distinguishing two stages characterized by an imbalance of sexual hormones in women and men. The secretin test was performed on 40 women and 47 men to evaluate the exocrine pancreatic function, taking age, as the central axis. In the group analyzed below the age of 45 there were no significant differences in the agreement with sex; but there were relevant differences between men and women above 45 years of age. The hormone secretin regulates the synthesis of lipase by interacting with the intrapancreatic cholinergic tone. When this is depressed, so does the debit of lipase. Pancreatic acini and islets have a high number of estrogen receptors, which activate and modulate the response of the gland to secretin, CCK and acetylcholine. Estrogen activates the beta cells stimulating the release of insulin, which enhances the exocrine secretion induced by CCK. We conclude

that during menopause the decrease in estradiol leads to less interaction with the secretin hormone receptors, which leads to a high percentage of dyspeptic syndrome, ultimately menopausal chronic pancreatopathy / menopausal pancreatic insufficiency. This is reversed with the administration of estradiol. In men older than 45 years we observed an increase in lipase secretion, a consequence of a hyperestrogenism caused by the aromatization of androgens. From clinical experience we observed the beneficial effect of citrate powder in patients with dyspeptic syndrome, gastritis and pancreatopathies, which demonstrate that they induce the release of secretin from the duodenal mucosa.

Key words. Secretin, plexus reticular, citrates, menopause.

Función del páncreas exocrino - sexo, edad, tono colinérgico y estrogénico - valor clínico preliminar de los citratos

Resumen

Este estudio pivotea en la secreción pancreática exocrina. Tomamos como eje los 45 años, distinguiendo dos estadios caracterizados por un desbalance de hormonas sexuales en mujeres y hombres. Se realizó el test de secretina a 40 mujeres y 47 hombres para evaluar la función pancreática exocrina, tomando como eje central, la edad. En el grupo analizado por debajo de los 45 años no demostró diferencias significa-

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tivas de acuerdo al sexo; si resultó ser relevante la diferencia entre hombres y mujeres por encima de 45 años. La hormona secretina regula la síntesis de lipasa interactuando con el tono colinérgico intrapancreático. Cuando este se deprime, también lo hace el débito de lipasa. Los acinos e islotes pancreáticos contienen un alto número de receptores estrogénicos, que se activan y modulan la respuesta de la glándula a la secretina, la CCK y la acetilcolina. El estrógeno activa las células beta estimulando la liberación de insulina, que potencia la secreción ecobólica inducida por la CCK. Concluimos que durante la menopausia la disminución del estradiol conduce a una menor interacción con los receptores de la hormona secretina, lo que deriva en un alto porcentaje de síndrome dispéptico, en última instancia, la pancreatitis crónica menopáusica/ insuficiencia pancreática menopáusica. Ello se revierte con la administración de estradiol. En el hombre mayor de 45 años observamos un incremento de la secreción de la lipasa, consecuencia de un hiperestrogenismo ocasionado por la aromatización de andrógenos. Desde la experiencia clínica observamos el efecto benéfico de los polvos de citrato en pacientes con síndrome dispéptico, gastritis y pancreatopatías, lo que demuestra que inducen la liberación de secretina desde la mucosa duodenal.

Palabras claves. Secretina, plexo reticular, citrato, menopausia.

Abbreviations

CEPS: Exocrine Pancreatic secretion.

NPF: Neural Plexual Freeway.

PVR: Peri-Vaterian region.

CB: Cicatricial barrier.

ICR: Ileum-cecal region.

AIW: Ascending-inhibitory wave.

This study pivots on human exocrine pancreatic secretion (EPS). We choose 45 years limit to distinguish two different stages of life, focusing on the sexual hormones that fall during menopause leading to loss normal estradiol potentiation of the cell membrane secretin receptors, which results in the development of a high percentage of dyspeptic syndrome and ultimately menopause chronic pancreatitis.

Secretin regulates the synthesis of lipase interacting with the intrapancreatic cholinergic tone. When this tone falls also does lipase output. The pancreas's cells contain a high number of estrogen receptors, which activate and modulate the gland's response to secretin, CCK and

acetylcholine. Menopausal women are typically characterized by a depress of EPS, which reverts after estradiol administration. Estrogen activates beta cells, stimulating insulin liberation, which potentiates the pancreon's CCK ecobolic secretion. The hyperestrogenism in men above 45 years old enhances lipase secretion.

Dr. Polak's citrates powder induces secretin release from the duodenal mucosa and we used them to treat clinical cases of gastritis syndrome, dyspepsia and pancreatopathies.

Material and methods

The study was performed in patients according to the guidelines of the World Medical Association Declaration of Helsinki. The analysis was carried out with the classical Dreiling test.¹⁻³ Starting in the sixties, at the Mount Sinai Hospital (N.Y), afterward at the Sarles Lab. (Marsella) and Clinicas Hospital (Buenos Aires), we were able to analyze the exocrine pancreatic secretion (EPS). The evaluation was done in 40 women and 47 men, stratified into three groups of subjects:

Two groups above 45 years, the first there were 20 tests in males, median age 55 years (range: 47-81) and the second, there were 18 tests in females, median age: 52 years (range: 45-62). The third serie under 45 years there were 26 tests in males, median age: 35 years (range: 21-44) and 20 in females, median age: 37 years (range: 24-43).^{4,5}

After duodenal intubation with a double lumen tube, gastric and duodenal juices were collected separately. Boots secretin was injected as a bolus at the standard dose of 1,0 U/kg. The duodenal aspirate was collected by intermittent suction over the next 80 minutes, divided into 10 minutes periods. The 80 minutes cumulative values were also analyzed. The hydrelatic and ecobolic responses were measured by the following parameters: volume (ml/10 min), HCO₃-meq/l, according to the titrimetric method with nitric acid (Lehmann),⁶ lipase concentration was determined by Lehmann's⁷ method and amylase concentration, in the secretory pool by the Jungen method.⁸

Results

Men and women above 45 years of age: The post-secretin collection data showed that in the women group values were consistently lower than those for men. Lipase activity (Figure 1) and output (Figure 2) showed statistically significant differences. In the cumulative 80 minutes values, in men and women, all measures were consistently lower for women than for men. Bicarbonate

output and volume values revealed statistically significant differences (Figure 3 and Figure 4).

Men and women under 45 years of age: Analysis of the values of all parameters, in each of the eight 10 min

periods, showed that there were not significant differences in the parameters flow, bicarbonate concentration and output of the duodenal juice collected after secretin intravenous stimulation.

Figure 1. Post-secretin secretory patterns of men vs. women over the age of 45, Lipase activity.

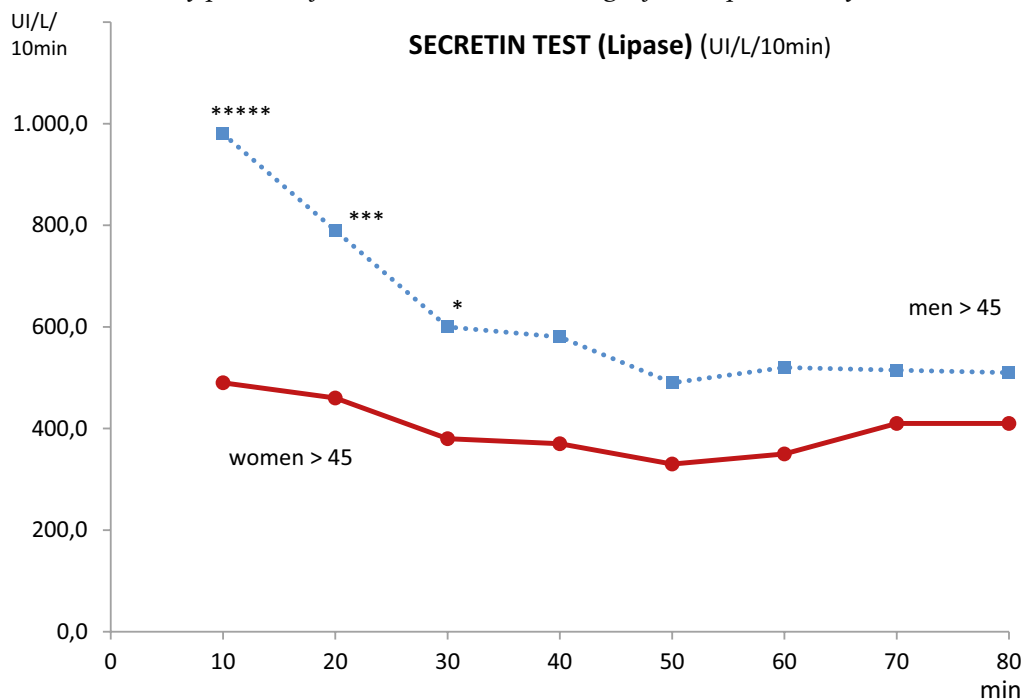


Figure 2. Post-secretin secretory patterns of men vs. women over the age of 45, Lipase output.

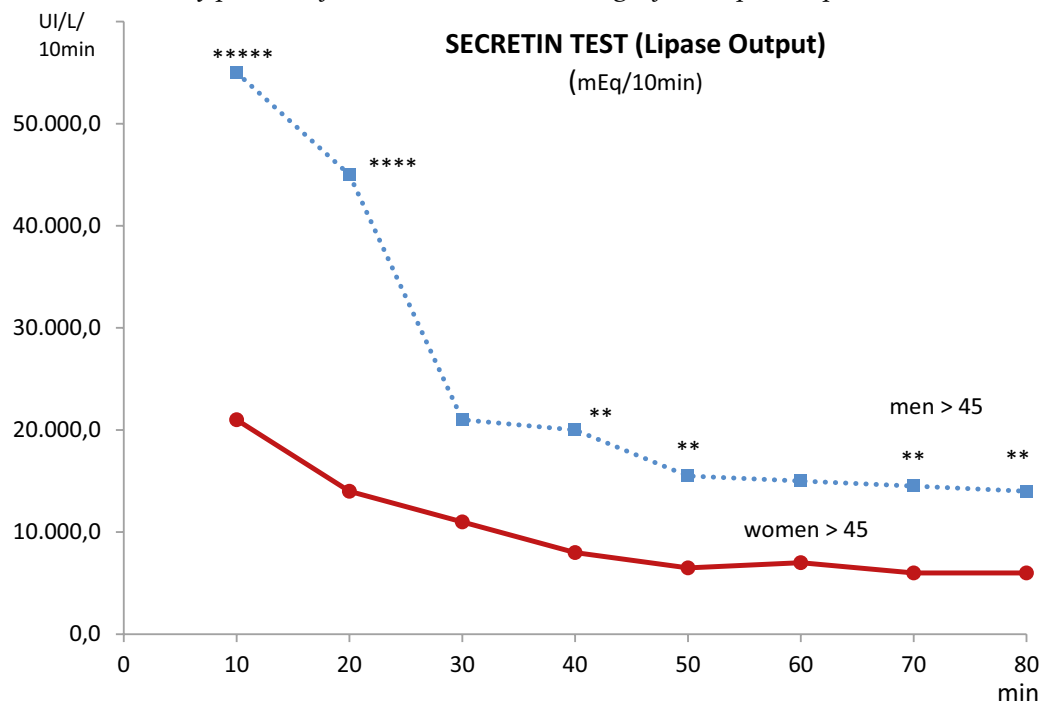


Figure 3. Post-secretin secretory patterns of men vs. women over the age of 45, Lipase activity.

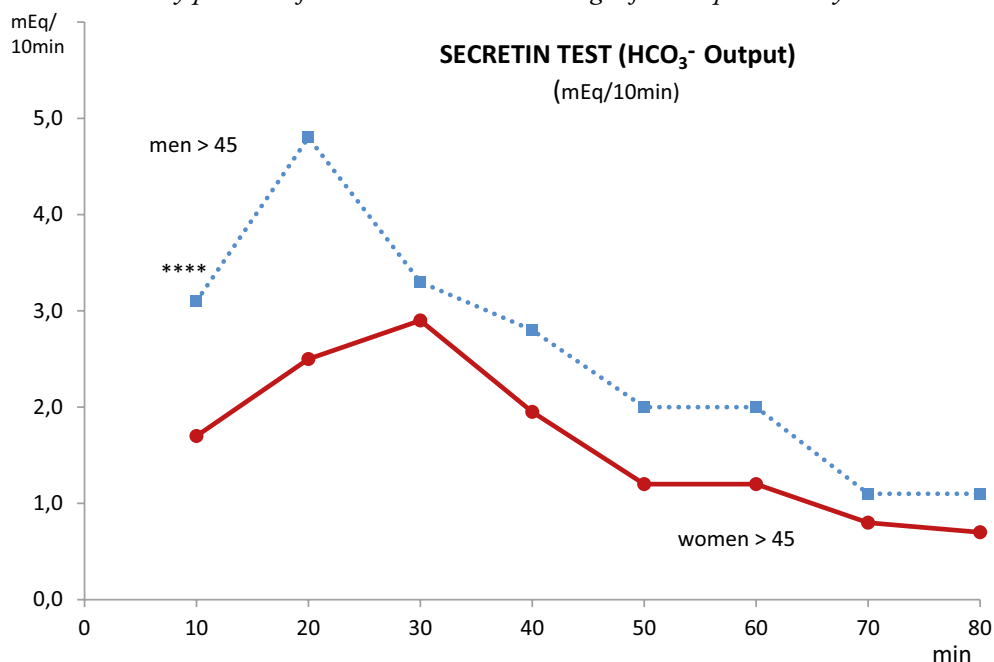
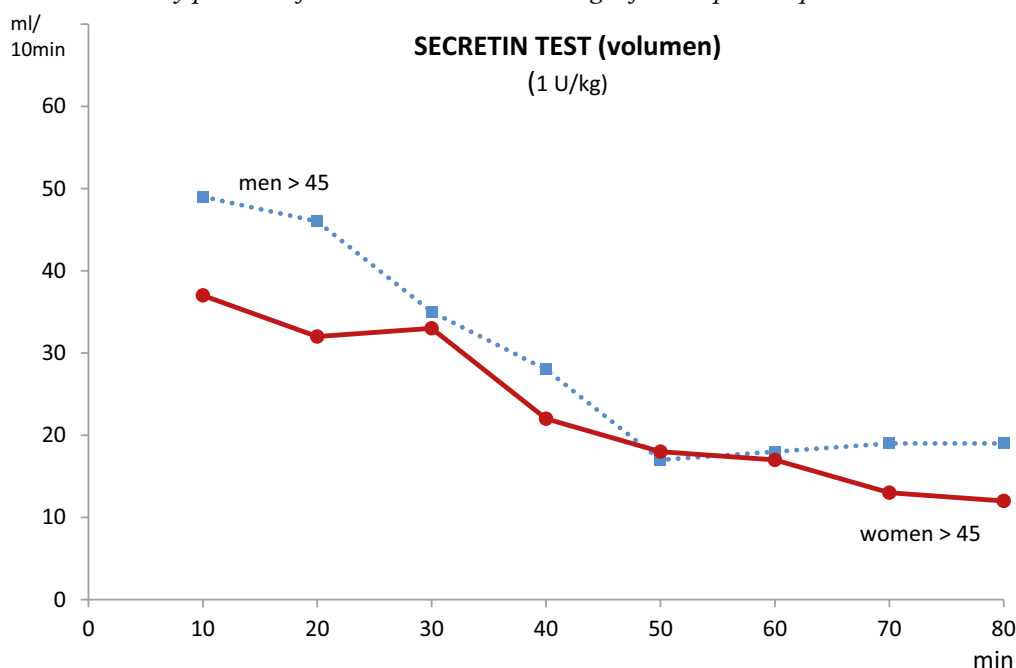


Figure 4. Post-secretin secretory patterns of men vs. women over the age of 45, Lipase output.



Discussion

The present findings confirm our previous observations¹⁻⁵ that in humans, the response of the exocrine pancreas to hormonal stimulation does show differences between

sex- and age-linked differences; these, in the pancreatic secretion were most notorious above 45 years. Fluid secretion tended to be greater in men than in women and it was significantly decrease in women overhead than 45 years.

The ecbolic function of the pancreas showed age and sex-dependent values for certain enzymes, especially lipase secretion was affected, but amylase was not.

The present results disclose that men above 45 years. have a greater post-secretin EPS than women; these are consistent with previous observations.

In Dreiling Lab, working with Hansky,⁹ we attempted to compare results between dogs and humans. Using 12 randomly selected normal subjects, six males and six females, we analyzed the response to a standard secretin test and found the mean peak 15-minute bicarbonate output to be 6.9 mEq in women and 8.8 mEq in men. The calculated bicarbonate output per gr of the human pancreas was 0.088 mEq/gr in females and 0.09 mEq/gr in males. This finding was consistent with the observation that a female dog excreted the same amount of bicarbonate (0.08 mEq/gr) as the human female did. Further analysis of the data indicated that bicarbonate output in men, per gram of gland, increases with age; in women were the inverse relationship develops.

In order to understand the behavior of pancreatic lipase, several findings should be taken into consideration. A crucial report was that of Rausch et al.,¹⁰ in the sense that secretin is the hormone who stimulates enzymes synthesize. This interaction takes place with the intrapancreatic cholinergic tone. When this fall, lipase output decline, the reverse is also true. Another feature to take into account is estrogen receptors are found in much higher number in the pancreas than other organs. Their activation modulates the response of the pancreas to secretin and CCK. Our findings with secretin in menopausal women, characterized by a depressed EPS, are reversed when estradiol is given to patients.¹¹⁻¹³

In order to get a better understanding of the pancreatic secretory changes linked to sex and age, is necessary to consider several physiologic findings, some of them well studied in the experimental animal. Concerning the lipase secretion, the secretin hormone plays a pivotal role. As it was already mentioned, this hormone is the main agent of synthesis and secretion stimulation in the pancreatic juice. Besides, the effects of the hormone are exerted interacting with the intra-pancreatic cholinergic tone and the one provided by the estradiol hormone. We have suggested an interplay develops between the secretin cells membrane receptors with those of the estrogen in the cytosol. In this type of assessment, performed in rats, we have pointed out that, the female hormone activated the beta cells of the Langerhans islets. The insulin hormone potentiated the "pancreon's" ecbolic secretion.

A feature to emphasize is the significative enhance lipase secretion in men above 45 years. in contrast to the absence of this difference in persons below this time limit. In respect to this finding, our postulation is that the physiologic mechanism is centered in the relative hyperestrogenism that develops in the men group with advancing age; that involves the following events sequence: a) the fall of testosterone secretion by the testis; b) the aromatization process of the androgenic agents; c) the potentiation of the whole sequence by alcohol feeding. The latter well explained by the fact that, chronic alcoholism induces a notorious enhancing of the number of estrogenic receptors, both in the liver and pancreas. This observation of our group was well taken by Gumaste as a suggestive index to point out the etiologic agent of an episode of acute pancreatitis.^{14, 15} This gets confirmation when an episode of acute pancreatitis reveals, in blood, a preferential rise of lipase vs amylase. This observation gives solid support to an alcoholic etiology.

Other observations, linking interrelations between estradiol, the synthesis and secretion of lipase, were referred by Hilgendorf et al.¹⁶ and Blevnis¹⁷. They showed that estradiol, impinging upon isolated acinar cells, induce enzyme secretion. This finding is associated with the histologic image of zymogen granules "trapped" in the acinar cytosol. This is in total contrast with those that are appreciated with the hormone CCK. In respect to the above findings, we consider that a feature deserving to be mentioned is the one we have observed in dogs subjected to supramaximal dosis of intravenous secretin. In these tests was surprising and notorious the picture of zymogen granules "trapped" against the apical membrane of the "pancreon" acinar cells.¹⁸ We got these findings in the Sarles Lab given further basis to the notion that the secretin hormone is the main agent that synthesize the lipase enzyme.

In the seventies, following Polak personal communication we designed a pharmaceutical prescription formula with a mixture of citrates, under advice of a pharmacologist.¹⁹ Those citrates, releasing secretin from the duodenum jejunal mucosa, elicit a series of positive changes upon the whole gastrointestinal tract. The main mechanism involved is the induction of a protective layer of mucus. At the level of the stomach and duodenum plays the substantial role of enhancing the protective mechanism against the injurious influences exerted by an excessive chloride acid secretion. We administrated this preparation during meals to patients with clinical cases of gastritis, syndrome dyspeptic and pancreatopathies. Another interestingly fact of benefit citrates effects is pre-

vented the duodeno-gastric and gastro-esophageal reflux elicited by the citrate-induced secretin. In addition to all the above facts, it deserves to be taken into account the excito-secretory role of the released secretin upon both; the hepatobiliary and exocrine pancreatic gland, conjunction with a cholinergic tone, those two secretions are essential to get an efficacious digestive process and a modulatory role upon both; the motility and chloride acid secretion of the stomach.

Another way, in this decade, we described, for the first time in the literature, by means of a macroscopic anatomic dissection that both; in human cadavers and in dogs and rats a duodeno-pancreatic-cleft-plexus (DPCP) is found. Subsequently, we were able to develop a conceptual synthesis of the neural plexual freeway (NPF).^{20, 21} Its distinctive quality is that of being functional even when disconnected from cephalic and spinal tract afferences following celiac ganglionectomy plus bilateral vagotomy. Its remarkable feature is that of its ganglion plexual reticular arrangement all along the gastro-intestinal tract; the latter similar to the one observed in the reticular tract, in the central nervous system (CNS).

The above facts justify assimilating the peculiarities of the entero-pancreatic innervation to those of a real "freeway", this mainly in the sense that the flow of neural impulses take place following precise "lanes" in search of different final objectives. Undoubtedly, a key region of what we have described as an NPF is the peri-Vaterian-region (PVR).²²⁻²⁵ Here many visceral neural fibers jump the duodeno-pancreatic-cleft to enter into the pancreatic gland. They are cholinergic and serotonergic exerting a modulatory influence upon the intra-pancreatic ganglia. A feature to emphasize is the presence of cholinergic "command neurons". In fact, it deserves to be considered a real parasympathetic nucleus. It derives from the "ventral primordio" of the pancreatic gland, source of the inferior segment of the head and of the "processus uncinatus". Subsequently, was known as the "hook", rich in Langerhans islets, with predominant PP cells.

Interfering the course of the NPF with "cicatrical barriers" (CB), induced by section and re-anastomosis of the intestinal wall, performed at certain elective zones, allowed to get valuable information of diverse characteristics. Thus, in the stomach, at the level of the antral fundus intersection", CB induced a peptic ulcer in the antrum. This surgical model of peptic ulcer evolved, in a good percentage of the cases, to an adenocarcinoma. The above findings led us to consider the "antral-fundus-junction" as the 1st modulatory center of the NPF.

When performing secretory studies in dogs, provided with several Thomas cannula: in the stomach, to divert gastric juice, in the duodenum to collect bile-pancreatic juice, in the ileum and cecum, to instillation oleic acid, with which we put in evidence a remarkable inhibitory phenome of bile-pancreatic secretion, we were able to delineate the 3rd modulatory center of the NPF, with epicenter in the ileum-cecal region (ICR).

In what concern to the peri-Vaterian region (PVR), this segment of the NPF, where we place the Thomas cannula in order to proceed to the cannulation of the bile-pancreatic duct, is considered the 2nd modulatory center of our NPF. When we decided to interfere with the flow of the neural impulses we appealed to CB, supra and infra-Vaterian; this allowed isolating the richest cholinergic PVR zone. At this level, is where we put in evidence, with our dissection, the highest density of neural fibers jumping the duodenum-pancreatic cleft.

When attempting a glimpse of the whole NPF, it is evident that one of its functions is that of slowing or stopping an unjustified energy wasting when the digestion process has reached the last stage. Speculating further, we have arrived to the conception of an "ascending inhibitor wave" (a.i.w) that exerts a modulatory influence upon the proximal autonomic centers. Thus a.i.v, after entering the hepatic bile tract, at the level of the P.V.R, modulates the autonomic tone of the hepatic gland. All the above allow to infer that, implanting an "infra-vaterian-cicatrical-barrier" might be able to prevent the entering, into the hepatic bile tract, of the ascending inhibitory wave and thus, according to our thinking, would favor the release of the Lutt's insulin sensitizing factor. The technical approach to prove or disprove the core of the hypothetical formulation, put above to definitive consideration, was applied to analysis in rats. As the results of our surgical evaluation were positive, it is logical to assume that we will have to wait up to obtain the ratification in humans. Surely, in the near future, there will be approaches to simplify bariatric surgery.²³

Conclusion

We conclude that, during menopause the decrease in estradiol leads to less interaction with the secretin hormone receptors, which leads to a high percentage of dyspeptic syndromes, ultimately menopausal chronic pancreatopathy/menopausal pancreatic insufficiency. This is reversed with the administration of estradiol.

Analyzing the response to a standard secretin test (1.0 U/kg) we concluded that, bicarbonate output per gram of gland in men increases with age, and decreases in women.

This inverse relationship is supported by men's feminization process in which testosterone levels decrease, and increase lipase secretion, a consequence of a hyperestrogenism caused by the aromatization of androgens.

From clinical experience we observed the beneficial effect of citrate powder in patients with dyspeptic syndrome, gastritis and pancreatopathies, demonstrating that they induce the release of secretin from the duodenal mucosa.

Conflict of interest. None.

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