PhD Thesis
Abstract

Epidemiological dimensions and clinical research on GastroEsophageal Reflux Disease (GERD)

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Introduction

Gastroesophageal reflux disease (GERD) and sleep apnoea syndrome (SAS) are two clinical entities commonly encountered in clinical practice. Lifestyle (stress, etc.) and eating habits (fast food, etc.) are two catalytic factors in the development and/or aggravation of these health issues. Both entities, GERD and SAS are represented by the «Iceberg phenomenon», where, the top of the iceberg is represented by a) patients with persistent symptoms, severe complications that require specialized treatment and often are admitted to the hospital, b) up to the sea level is represented the number of patients with persistent symptoms which, sometimes, need a medical advice in order to be resolved and c) below the sea level there are patients with mild, sporadic symptomatology that usually do not require medical attention and, in fact, is the largest number of patients with GERD and/or SAS, which remains unknown to doctors. Iceberg phenomenon is a metaphor, emphasizing that, for almost every health issue, the number of known cases of disease is compensated by those that remain undiscovered, most often the unseen part of an «iceberg» is much larger than the part that is visible above the water level.

The current PhD Thesis entitled «Epidemiological dimensions and clinical research on Gastroesophageal Reflux Disease» addresses to common, aggravating factors between these two clinical entities. The main objective of this work is the development and evaluation of a possible treatment that relieves/treats the symptomatology of both gastroesophageal reflux disease and obstructive sleep apnoea syndrome (OSAS).

The current PhD Thesis is divided into two main parts. The first part consists of three chapters, which contain general concepts on the epidemiological data and treatment of GERD and general notions of literature for the correlation between GERD and OSAS. The second part of the research which consists of personal contributions, contains original results about GERD and numerous results using the Epworth Sleepiness Scale questionnaire and complete polysomnography to assess the prevalence of OSAS and the clinical and statistical correlation with GERD. Although extensive and well documented, this study can not completely cover and involve the wide range of all the parameters.
that lead to the occurrence of GERD and OSAS. It is dedicated on possible treatments which can be used to relieve the symptoms of patients with GERD and OSAS and for a better understanding of these two health issues.

**Objective:** to conduct clinical studies to highlight the existence of relations between gastroesophageal reflux disease and obstructive sleep apnoea syndrome and to establish useful recommendations in clinical practice.

The main objectives are represented by the study of sensitivity and specificity of GERDQ (Questionnaire), which is an instrument for the evaluation of gastroesophageal reflux disease in patients without undergoing upper gastrointestinal endoscopy and in fact for the evaluation of presence or not of esophagitis. Also, this study, assesses the prevalence of the obstructive sleep apnoea syndrome and gastroesophageal reflux disease and the risk factors that exist for each of the two clinical entities.

Finally, we study the common factors between these two clinical entities that can worsen the patient’s health condition (for worsening the obstructive sleep apnoea syndrome or worsening of the gastroesophageal reflux).

The major and most important question that tries to be answered is: If we relieve the symptomatology of the obstructive sleep apnoea, can this be helpful in relieving the symptoms of gastroesophageal reflux?

**Associate objectives** took into account the following aspects:

1. Statistical characterization of the lot
2. To determine the frequency of OSAS in men and women by using the Epworth Sleepiness Scale Questionnaire and also to determine the frequency of GERD in men and women
3. To determine the frequency of OSAS and GERD in the general population (to the point that these patients although they had the typical symptoms of the two
clinical entities, have not been to a doctor and seek medical attention)
4. To determine the risk factors that may cause or influence the evolution to GERD and OSAS of may even worsen/complicate the diagnostic status of patients with these clinical entities
5. To study possible correlations between some of the risk factors that contribute to the appearance of GERD and OSAS
6. To determine the risk factors that have a higher prevalence or aggression in the context of these two entities
7. Establishment of socio-economic criteria that can lead to these diseases.

Materials and Methods

In this study, have been included and evaluated three different groups of subjects/patients:

1. 200 people of both sexes from the general population to whom the Epworth Sleepiness Scale and Gastroesophageal Reflux Disease questionnaire has been applied in January 2008 – March 2011. Of the 200 people, six refused to participate in the study.
2. Also during this period, in a gastroenterology hospital in Greece, specially trained doctors recruited subjects for inclusion in the study of a number of 426 people already hospitalized or examined by upper gastrointestinal endoscopy after presenting symptoms of gastroesophageal reflux disease. Twenty patients refused to participate in the study.
3. Finally, 337 patients diagnosed with OSAS have been tested for BRGE and in case they suffered from both entities, tried to find any correlations between them (University Hospital of Ioannina, polysomnography Center).
- Epworth Sleepiness Scale Questionnaire (ESS)
- GastroEsophageal Reflux Disease Questionnaire (GERDQ)
- Polysomnography

Figure 1: Polysomnographic recording
- Upper gastrointestinal endoscopy

- Statistical methods

The results are presented as mean ± standard deviation (SD). Statistical analysis were performed using SPSS 20.0 software (IBM). Bilateral T-test was used to compare the measurements obtained with and without nCPAP during sleep. Linear regression analysis were used to determine correlations between classes of gastroesophageal reflux and sleep variables. Prevalence rates were calculated for esophagitis, gastritis, Barrett’s esophagus, hiatal hernia and gastroesophageal flap valve abnormalities. Age, male to female ratio, the presence of hiatal hernia, the degree of injury to the esophageal mucosa using the Los Angeles classification. The various categories of symptoms were compared between groups with grades of normal and abnormal gastroesophageal flap valve using one-sided t-test. \( \chi^2 \) test was conducted to evaluate classes of normal and abnormal gastroesophageal flap valve. Several comparative tests were conducted among groups of esophageal mucosal injury. A p value <0.05 was considered to be statistically significant for a confidence interval of 95%.

Results

Figure IV.60 shows a chart with the number of patients who were included in the study. 337 patients were diagnosed with the obstructive sleep apnoea syndrome, 194 patients had no gastroesophageal reflux disease. 143 patients had positive diagnosis of obstructive sleep apnoea syndrome plus gastroesophageal reflux disease. In the 143 patients had been prescribed nCPAP at home and they were instructed to use the equipment every night for a six-month period. After this period they came back for control undergoing a new polysomnographic recording for a second time. 66 patients didn’t come for a second polysomnographic check so only 77 of them reappeared of which 58 mentioned amelioration of the symptomatology of GERD and 19 haven’t seen any improvement.
Correlations between various measured parameters

Male/female correlations

Males:

- Smoke more than women in the current study $r=0.319$ and $p=0.005$.
- AHI score is higher $r=0.242$ and $p=0.034$,
- Snoring is more prevalent in males ($r=0.286$, $p=0.012$)
also, hypertrophied tonsils are more common between males 
\((r=0.281, p=0.013)\).

Correlations by group of age

Nocturia is more prevalent in the elderly patients 
\((r=0.292, p=0.010)\).

Correlations by the number of packs of cigarettes consumed per year

Men, smoked significantly more than women 
\((r=0.319, p=0.005)\), as the use of cigarette smoking is higher so:

- AHI score seems to get higher 
  \((r=0.283, p=0.013)\),
- Periods of sleep apnoeas seem to be more frequent 
  \((r=0.345, p=0.002)\),

Figure IV.98: Snoring between sexes (male/female).
- Haemoglobin desaturation 4% seems to be more frequent ($r=0.342, p=0.002$)
- Tachycardias seem to be significantly more frequent ($r=0.255, p=0.025$).

Heavy smokers after using nCPAP had a negative correlation with smoking ($r=-0.400, p<0.001$) and SpO$_2$ ($r=-0.414, p<0.001$) meaning that there is a bigger improvement in patients who smoke much than patients who do not smoke or smoke less.

**Correlations by BMI**

Patients with increased BMI score were less likely to suffer from daytime headaches ($r=-0.247, p=0.03$) but:

- Have a higher AHI score ($r=0.483, p<0.001$),
- Their neck circumference is bigger ($r=0.366, p=0.001$),
- Have been observed more apnoeic episodes during sleep ($r=0.276, p=0.015$)
- And also, more episodes of haemoglobin desaturation ($r=0.342, p=0.002$).

Patients with higher BMI score, after using nCPAP had a negative correlation with SpO$_2$ during sleep ($r= -0.319, p= 0.005$) meaning that there is a bigger improvement in patients who are more obese than patients with normal BMI.

Correlations by AHI score

AHI score found to be higher in males ($r=0.242, p=0.034$) and it is correlated with:

- The number of smoked cigarettes ($r=0.283, p=0.013$),
- High BMI score ($r=0.483, p<0.001$)
- Neck circumference ($r=0.267, p=0.019$).

Here, it is noted the importance of the correlation between the AHI score and:
- Number of apnoeic periods \( (r=0.715, p<0.001) \),
- Number of haemoglobin desaturations \( (r=0.692, p<0.01) \),
- Number of tachycardias that appear during sleep \( (r=0.294, p=0.010) \)
- and the number of arousals during sleep \( (r=0.322, p=0.004) \).

A negative correlation between AHI and SpO2 has been observed \( (r=-0.474, p<0.001) \).

Figure IV.101: Sensation of suffocation during sleep between sexes.
Correlations with snoring (Figure IV.98)

The only correlation that has been observed is linked to the sex of the patients with men showing a higher frequency of that symptom than women ($r=0.286, p=0.012$).

Correlations with nocturia (Figure IV.99)

Patients that present more apnoeic episodes ($r=0.247, p=0.031$) or they are elderly ($r=0.292, p=0.01$), present with nocturia more frequently than younger patients.

Correlations with daytime headache (Figure IV.100)
Patients with high BMI score are less likely to have daytime headaches \((r= -0.247, p=0.03)\) but those who present with more apnoeic episodes during sleep are more likely to experience daytime headaches \((r=0.251, p=0.027)\).

**Correlations with a sense of suffocation during sleep (Figure IV.101)**

It has been found that there is a correlation between the big volume of the tonsils and the sensation of suffocation during sleep \((r=0.262, p=0.021)\).

**Correlation by the neck circumference (Figure IV.102)**

It has been found that there is correlation between neck circumference and:

- BMI \((r=0.366, p=0.001)\),
- AHI score \((r=0.267, p=0.019)\),
- Big volume of the patients’ tonsils \((r=0.237, p=0.038)\),
- Total number of the apnoeic episodes \((r=0.284, p=0.012)\),
- Haemoglobin desaturation \((r=0.240, p=0.035)\)
- Has been found a negative correlation between the neck circumference and SpO\(_2\) \((r=0.328, p=0.004)\).

**Correlations with the volume of tonsils (Figure IV.103)**

It has been found that there is correlation between the volume of the patient’s tonsils and:

- Sex (male) \((r=0.281, p=0.013)\),
- Sensation of suffocation during sleep \((r=0.262, p=0.021)\),
- Neck circumference \((r=0.237, p=0.038)\)
- And negative correlation with SpO\(_2\) \((r= -0.349, p=0.002)\).
Correlations with the total number of apnoeic periods during sleep

Positive correlations between the total number of apnoeic periods and:

- The number of the smoked cigarettes \((r=0.345, p=0.002)\),
- Level of obesity \((r=0.276, p=0.015)\),
- AHI score \((r=0.715, p<0.001)\),
- Neck circumference \((r=0.284, p=0.012)\),
- Haemoglobin desaturation \((r=0.925, p<0.001)\),
- Number of tachycardias \((r=0.419, p<0.001)\),
- Number of bradycardias \((r=0.336, p=0.003)\),
- Number of arousals during sleep \((r=0.588, p<0.001)\).

A negative correlation found to exist between the total number of apnoeic periods and \(\text{SpO}_2\) \((r=-0.501, p<0.001)\).

Correlations with haemoglobin desaturation 4%

Positive correlations with:

- The number of the smoked cigarettes \((r=0.342, p=0.002)\),
- Body weight \((r=0.281, p=0.013)\),
- AHI score \((r=0.692, p<0.001)\),
- Neck circumference \((r=0.240, p=0.035)\),
- Total number of the apnoeic periods \((r=0.925, p<0.001)\),
- Number of tachycardias \((r=0.456, p<0.001)\),
- Number of bradycardias \((r=0.332, p=0.003)\),
- Number of arousals during sleep \((r=0.681, p<0.001)\).

A negative correlation found to exist between haemoglobin desaturation 4% and \(\text{SpO}_2\) \((r=-0.502, p<0.001)\).

Correlations with the tachycardic episodes during sleep

Tachycardias are more frequent when:

- Patients are heavy smokers \((r=0.255, p=0.025)\),
- Have high AHI score ($r=0.294, p=0.01$),
- The total number of apnoeas is high ($r=0.419, p<0.001$),
- Haemoglobin desaturation is frequent ($r=0.456, p<0.001$),
- Bradycardias are frequent during sleep ($r=0.51, p<0.001$),
- The number of arousals during sleep is high ($r=0.473, p<0.001$),
- And finally when the SpO$_2$ level is low ($r=-0.379, p<0.001$).

**Correlations with the bradycardic episodes during sleep**

Bradycardias are more frequent when:

- The total number of apnoeas is high ($r=0.336, p=0.003$)
- Haemoglobin desaturation is frequent ($r=0.332, p=0.003$),
- The number of arousals during sleep is high ($r=0.434, p<0.001$),
- Tachycardic episodes are also present ($r=0.510, p<0.001$)
- And finally when the SpO$_2$ level is low ($r=-0.318, p=0.005$).

**Correlations with the number of arousals during sleep**

A patient is more likely to wake up (arousals) several times during sleep when:

- AHI score is high ($r=0.322, p=0.004$),
- The total number of apnoeas is high ($r=0.588, p<0.001$),
- Haemoglobin desaturation is frequent ($r=0.681, p<0.001$),
- Tachycardias are frequent during sleep ($r=0.473, p<0.001$),
- Bradycardias are frequent during sleep ($r=0.434, p<0.001$)
- And when the SpO$_2$ level is in the lower limits ($r=-0.366, p=0.001$).

As previously mentioned, from 337 patients with sleep apnoea syndrome, 194 had no gastroesophageal reflux disease. 143 patients had sleep apnoea syndrome and gastroesophageal reflux disease and were eligible for this study. Of those (143), 66 were not included to a new polysomnographic recording due to the fact that they didn’t
appear after six months of the treatment (with nCPAP device at home).
77 patients came back for a 2nd polysomnographic recording. 58 of those had an improvement of the symptomatology of GERD and 19 did not report a significant improvement or they didn’t have an improvement of their symptoms at all.
Conclusions

1. There is correlation between gastroesophageal reflux disease and obstructive sleep apnoea syndrome because it has been demonstrated that amelioration of the symptomatology of OSAS leads to GERD symptom relief.

2. The typical profile of patients with obstructive sleep apnoea syndrome is with the following characteristics: hypertrophied tonsils, short neck, male, smoking, high BMI. Results from this study affirm the results of previous studies.

3. Sleep apnoea severity is indicated by AHI score, the degree of the haemoglobin desaturation and the high incidence of heart arrhythmia episodes (tachycardia/bradycardia).

4. Men are at increased risk of developing gastroesophageal reflux disease and obstructive sleep apnoea syndrome.

5. The use of nCPAP in patients with coexisting gastroesophageal reflux disease and obstructive sleep apnoea syndrome leads to symptom improvement of both clinical entities.

6. There is correlation between gastroesophageal valve deformity and severity of gastroesophageal reflux disease.

7. Prevalence of gastroesophageal reflux disease is higher in men than in women. Prevalence of esophagitis between the two sexes is double (Los Angeles C – male/female: 65,9%/34,1%) or triple (Los Angeles D – male/female: 72,4%/27,6%) and the deformity of the gastroesophageal flap valve seems to be double between sexes (male/female: 13,6%/6,4%).

8. Hiatus hernia occurs more frequently in males.
9. Likelihood of association between GERD and OSAS is greater in obese patients.

10. Patients, who used nCPAP equipment, had fewer heart arrhythmia episodes (in the 2nd overnight measurement) compared to the 1st overnight polysomnography (with no nCPAP equipment).

11. After using the nCPAP device, AHI score, SpO₂, haemoglobin desaturation and nocturnal awakenings, normalized in a number of cases.

12. The AHI score is increased when the degree of gastroesophageal reflux disease is more severe.

13. By treating episodes of sleep apnoea, there is amelioration of gastroesophageal reflux symptomatology.
Discussion

The current study shows that there is an association between gastroesophageal reflux disease and obstructive sleep apnoea syndrome. Since this idea appeared, that there may be an association between the two clinical entities by Sullivan et al. several studies have been done to detect the association. The mechanism of action of nCPAP is based on maintaining a positive pressure in the upper airways during sleep period, which does not, permits them to collapse. Kerr et al. studied a group of patients with gastroesophageal reflux disease and sleep apnoea syndrome and showed that using CPAP machinery obtained the following results:
- During the first overnight recording, he didn’t use nCPAP and five out of six patients presented gastroesophageal reflux.
- During the second overnight recording, he used nCPAP and five out of six patients didn’t present gastroesophageal reflux.
Then, came to the result that there is a correlation between gastroesophageal reflux disease and sleep apnoea syndrome without any direct effect. Green et al. showed that after using the nCPAP machine in patients with GERD there was a significant improvement in >48% of those patients and the greater was the pressure of nCPAP device the best results obtained (48-86%). In our study, significant improvement in GERD patients reached 75%.

Patients with gastroesophageal reflux disease and obstructive sleep apnoea syndrome suffer from daytime headaches. In our study, 15,6% had daytime headaches but there are studies that show daytime headaches up to 48% (Prehn et al.). In another study by this researcher (Prehn, Simmons et al.), showed that 54% of those patients suffered from daytime headaches.

Choking during sleep is another symptom that occurs in patients with GERD and OSAS. In the current study 58,4% of patients reported this symptom in sleep and in other studies (Prehn et al.), this proportion reached 60%.

Snoring is common in patients suffering from GERD and OSAS. Although not all snorers have sleep apnoea, snoring is a cardinal symptom of OSAS. Snoring was present in 93,5% of the patients in
our study but was the cardinal symptom in other studies (*Schmidt – Nowara et al.*).

Nocturia is another characteristic symptom of OSAS. 67.5% of patients reported that they got out of bed for more than 2 times during sleep. There are many studies which refer to this symptom (which is quite prevalent) but no specific data showing an exact percentage.

Patients who have short and thick neck are more prone to present OSAS. In this study, these patients were in a proportion of 72.7%. Neck circumference along with body mass index are important factors for OSAS prediction.

*Davies et al.* attempted to show that only the neck circumference may be a factor for establishing the diagnosis of OSAS but came to the conclusion that it is not enough without a polysomnographic study.

Hypertrophic palatine tonsils is a factor that increases the severity of obstructive sleep apnoea syndrome and further increase of gastroesophageal reflux episodes. In our study, patients who had gastroesophageal reflux disease and obstructive sleep apnoea syndrome presented at 70.1% hypetrophied palatine tonsils.

*Moser et al.* demonstrated that patients with hypertrophied tonsils that underwent tonsillectomy had better outcomes when it comes about the OSAS in a percentage up to 70% of them.

*Martinho et al.* performed preoperative and postoperative polysomnography in patients with hypertrophied tonsils and concluded that AHI score was 81±26 and 23±18 pre- and post-operative respectively with SpO² 69±14% and 83±3% respectively.

Another very important factor is the cardiac arrhythmias. In the present study 72.7% had tachycardias during sleep and 36% had bradycardias. At this point, we did not go deeper in other heart arrhythmias as it is more complex and this is not the subject of our study. This can be done at another more specific study to find out more details about the arrhythmias during sleep in patients that suffer from OSAS. In literature there are many studies that show a correlation between OSAS and cardiac arrhythmias and between GERD and arrhythmias.

*Gerson et al.* demonstrated by polysomnographic recordings, 24h Holter and measurements of the pH (pHmetry), that patients who
were treated with PPI’s had less episodes of heart arrhythmias than those with no medical treatment. 

Obesity is a common factor between gastroesophageal reflux disease and obstructive sleep apnoea syndrome. Patients who presented GERD and OSAS in this study were mostly overweight (29.4%) with grade I obesity 32.9%, grade II obesity 24% and morbid obesity 9.8%. Only 3.9% of our patients were within the normal range of body mass index (18.5 to 24.9 kg/m²).

Escudero et al. associates gastroesophageal reflux disease with obesity by the increasing intraabdominal pressure, hypotonia of the lower esophageal sphincter and the presence of hiatal hernia. Hampel et al. realised a meta-analysis of nine studies and found that gastroesophageal reflux disease and its complications have a high correlation with the degree of obesity. Grimm et al. demonstrated that obesity is directly related to sleep apnoea and more specifically, patients with body mass index higher than 30kg/m² have a 50% chance of presenting with obstructive sleep apnoea syndrome.

Patients with gastroesophageal reflux disease and obstructive sleep apnoea syndrome had two overnight polysomnographic recordings, the first was before using the nCPAP equipment and the second after using nCPAP. During the first measurement AHI score was between 15 and 110 (average AHI score 60.74 and SD ±22.59). During the second measurement AHI score was between 2 and 66 (average AHI score 11.61 and SD ± 11.96).

Javaher described similar results with significant reduction of AHI score after the use of nCPAP.

McArdle et al. demonstrated that the use of nCPAP improves the symptoms of sleep apnoea syndrome and studied the patient compliance with the equipment that the patient does not easily accept it.

The number of apnoeas decreases with the use of nCPAP and this has as a consequence of reducing the number of episodes of gastroesophageal reflux during sleep time. In our study during the first overnight measurement the apnoeas were between 21 and 619 (average score 294.42 and SD 131.29). During the second overnight measurement the apnoeas were between 0 and 250 (average score 47.36).
Barone et al. demonstrated that the use of nCPAP equipment decreases the number of apnoeas but took a step forward showing that if nCPAP treatment stops only for one night may lead to recurrence of sleep apnoeas. The number of apnoeas and AHI score is not so high like before applying an nCPAP equipment because the upper airways are improved in terms of the oedema, but stopping for longer time leads to the same level of apnoeas and AHI score as before nCPAP treatment.

Krieger et al. observed patients with obstructive sleep apnoea syndrome over a long period of time (554 ± 28 days) that have been using nCPAP equipment at home. He demonstrated that using nCPAP devices increases the possibilities of a better sleep with less daytime complications (headaches, sleepiness etc.).

Gastroesophageal reflux disease is a clinical entity that decreases the quality of life of the patient in his everyday events. nCPAP treatment in patients who suffer from GERD and OSAS improves significantly their everyday quality of life.
Perspectives

Correlation between gastroesophageal reflux disease and sleep apnoea syndrome is not a new topic in research. The current study shows that treating GERD or improving the symptomatology of GERD drives to the conclusion that there is improvement in the symptomatology of both clinical entities (GERD and OSAS).

Although the pathophysiological mechanisms are not elucidated so far by the other studies, we have tried to give a solution and a perspective to a better quality of life for those suffering often from the typical symptoms of gastroesophageal reflux.

The way we present the treatment is promising but is not suitable for all patients suffering from this disease.

Also, as shown in the results, it is a solution that improves the results by using nCPAP but we do not have to forget that it is necessary to change the lifestyle of patients who suffer from these clinical entities. Patients with high BMI (body mass index) are considered of having an additional preexisting pathology that influences their quality of life.

We believe that the current study results are an additional database source for further research on this area of pathology that is encountered in clinical practice.
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