

Research Article

Thyroid Axis Functioning in Patients with High Suicide Risk

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Abstract

Background: The aim of this study was to evaluate thyroid axis functioning in patients, hospitalized due to high suicide risk.

Methods: Adults non-psychotic patients, without organic brain disorder, hospitalized due to high suicide risk were invited into this study; 56 patients signed consent form. They filled the sociodemographic questionnaire, the Hospital Anxiety and Depression scale (HAD) and blood samples were assessed for Thyroid Stimulating Hormone (TSH), Free Thyroxine (FT4) and Free Triiodothyronine (FT3) concentrations. Blood samples of 120 donors were used as controls.

Results: Of all patients - 83.9% were hospitalized after suicidal attempt and 16.1% due to severe suicidal ideation. The younger patients were more likely commit suicide attempt, than older patients group ($p=0.033$); with no differences according gender. Only 23.2% of patients were diagnosed with a depressive disorder; 62.5% - with adjustment disorder and 14.3% - with alcohol abuse. The comparison of thyroid axis hormones concentrations among euthyroid patients and controls revealed that the patients had significantly lower mean FT3 concentrations (4.02 ± 0.85 pmol/l vs. 5.17 ± 0.81 pmol/l, respectively; $p < 0.001$) and significantly lower mean FT4 concentrations (13.60 ± 2.65 pmol/l vs. 16.73 ± 2.23 pmol/l; $p < 0.001$), without significant differences in TSH concentrations. The older age showed positive correlation with severity of depressive symptoms ($r=0.313$, $p=0.024$) and negative correlation with FT4 concentration ($r= - 0.181$; $p=0.021$). Lower concentrations of TSH related with higher severity of depressive ($r= -0.478$; $p < 0.001$), but not anxiety symptoms.

Conclusion: Patients with high suicide risk had lower free thyroid hormones concentrations, without differences in thyroid hormone activity in the pituitary.

Keywords: Suicide risk; Thyroid hormones; Anxiety symptoms; Depressive symptoms

Introduction

According to World Health Organization (WHO) suicide is recognized as a major public health problem and there were an estimated 788000 suicide deaths in 2015 worldwide [1]. Moreover, suicide ranks among the main health problems in Lithuania. The Health information center of Lithuanian, Hygiene Institute "indicated that 823 people committed suicide in 2016 and suicide rate was 28.7 per 100 000 inhabitants [2]. This is the highest rate in the European Union. Therefore the analysis of suicide risk factors remains an important public health task.

Various factors related to the high risk of suicidal behavior are considered. A Danish study in 2003 processed the data from four national longitudinal registers and 21169 persons who committed suicide in 1981-1997 and showed that suicide risk is strongly associated with mental illness, unemployment, low income, marital status, and family history of suicide; the effect of most risk factors differs significantly by gender [3]. The prospective study in the USA evaluated 6891 psychiatric outpatients at the Center for Cognitive Therapy (CCT) of the University of Pennsylvania between 1975 and 1995 and indicated several modifiable significant and unique

risk factors for suicide, including suicide ideation, major depressive disorder, bipolar disorder, and unemployment status [4]. A total of 84850 adults were interviewed regarding suicidal behaviors, socio-demographic and psychiatric risk factors: the data from the WHO World Mental Health (WMH) Survey Initiative. Consistent cross-national risk factors included being female, younger, less educated, unmarried and having a mental disorder. The strongest diagnostic risk factors were mood disorders in high-income countries, but impulse control disorders in countries with low and middle income [5].

To evaluate all factors of suicidal behaviors and to predict the suicide is difficult due to the low base rate, even in high-risk groups, and the multi-causal nature of the suicidal behavior. While clinical predictors have shown low specificity, in the neurobiology of suicide the abnormalities of serotonergic mechanism, receptor-linked signaling mechanisms, neuroimmune and endocrine functions are discussed [6]. It is known that Hypothalamic-Pituitary-Thyroid (HPT) axis hormones are important for the human body metabolism, changes in hormones concentrations could affect a patient's psychiatric and neurologic status [7,8]. The most commonly

Table 1: Sociodemographics characteristics of study participants.

| | | Patients, n=56 | Controls, n=120 | P vs C |
|--------------------------------|----------------------------|----------------|-----------------|---------|
| Mean age, years | | 36.46±13.13 | 34.31±12.96 | p=0.307 |
| Age groups, years, n (%) | 18-28 | 18 (33.3) | | |
| | 29-43 | 19 (33.4) | | |
| | 44-66 | 19 (33.4) | | |
| Gender, n (%) | male | 19 (33.9) | 69 (57.5) | p=0.003 |
| | female | 37 (66.1) | 51 (42.5) | |
| Psychiatric diagnoses, n (%) | Adjustment disorder | 35 (62.5) | - | |
| | Depressive disorder | 13 (23.2) | - | |
| Severity of affective symptoms | Alcohol abuse | 8 (14.3) | - | |
| | HAD-D subscale, mean score | 6.73 ± 4.64 | - | |
| | HAD-A subscale, mean score | 10.64 ± 4.76 | - | |
| Suicidality, n (%) | Suicidal ideations | 9 (16.1) | - | |
| | Suicidal attempt | 47 (83.9) | - | |

HAD-D: Hospital Anxiety and Depression scale, Depression subscale; HAD-A: Hospital Anxiety and Depression scale, Anxiety subscale; P: patients; C: controls.

documented abnormalities, related to psychiatric symptoms were elevated Thyroxine [T4], low Triiodothyronine [T3], elevated reverse Triiodothyronine [rT3] concentrations, a blunted Thyroid Stimulating Hormone (TSH) response to Thyrotropin-Releasing Hormone [TRH], positive antithyroid antibodies, and elevated Corticotropin-Releasing Factor (CRF) TRH concentrations [9]. The thyroid dysfunction is associated with affective and psychotic disorders [10-12]. Thyroid function plays an important role in predicting the response to the treatment of major depression and bipolar disorder [13], augmentation with thyroid hormone has therapeutic efficacy in treatment-resistant depression [14] and in acute schizophrenia [15]. The effect of thyroid hormone concentration on suicidal behavior is being investigated more in recent years, but data remains contradictory.

The aim of this prospective study was to evaluate associations between sociodemographic factors, the severity of affective symptoms and thyroid axis functioning in patients, hospitalized due to high suicide risk.

Material and Methods

Study population

This prospective study was performed in the Psychiatry Department of Lithuanian University of Health Sciences (LUHS) hospital Kaunas Clinics from November 2016 until July 2017. The Bioethics Committee of the LUHS, Kaunas, Lithuania, approved the study and its consent procedures (Permission No.: BEC- LSMU (R)-05; 2015-09-24). All adults, non-psychotic patients, without a diagnosis of organic brain disorders and significant cognitive impairment, consecutive hospitalized to Psychiatry Department due to high suicide risk were invited to participate in this study. Of 75 hospitalized patients, 56 patients, 18 to 66 years old (response rate 74.6%) agreed to participate and signed an informed consent form.

The control group consisted of 120 consecutive healthy donors, 18 to 62 years old (without a history of mental disorders or suicide attempts) from Kaunas Donation center, Lithuania (permission of Kaunas Regional Biomedical Research Ethics committee, Nr.BE-2-17;

2009-10-12).

Methods

All study participants were invited to fill out the authors' composed socio-demographic questionnaire. It consisted of questions about patient's age, gender, concurrent somatic diseases, history and type of suicidal ideations or behavior.

Hospital Anxiety and Depression scale (HAD) was used to determine the severity of anxiety and depressive symptoms. The HAD scale is a self-reported instrument and consists of 14 questions, each with four answers, 0 to 3 points respectively. Seven items for the evaluation of depressive symptoms and their severity (HAD-D) and seven items for anxiety symptoms and their severity (HAD-A) [16]. The scores of depressive and anxiety symptoms in the group can range from 0 to 21. Grading scores indicate a degree of depressive or degree of anxiety symptoms: from 0 to 7 points - normal anxiety or mood; from 8 to 10 points - mild; 11 to 14 points-moderate; and from 15 to 21 points are severe symptoms of anxiety or depression.

On the day of hospitalization the blood samples were taken from the study patients to determine thyroid axis hormone concentrations - (TSH, Free Thyroxine (FT4) and Free Triiodothyronine (FT3). Blood samples of 120 blood donors were used for control comparison.

Statistical analysis

A statistical analysis was performed using the IBM SPSS Statistics 23.0. All continuous data were represented as the mean and Standard Deviation (SD), all categorical data- as numbers and percentages. The frequency rates were compared by chi-square test, two independent sampling averages - Oneway ANOVA. The correlation among variables was performed by using Spearman correlation coefficient. The statistical significance level in the study was $\alpha = 0.05$, and the 95% confidence interval was used.

Results

Sociodemographics characteristics of all study participants are presented in Table 1. Comparison of two groups revealed that there were no significant mean age differences among study patients

Table 2: The comparison of thyroid axis hormone concentrations in euthyroid hospitalized patients with high suicide risk and donors - controls.

| | Patients, n=52 | Controls, n=110 | Oneway ANOVA | Normal range |
|-------------|----------------|-----------------|------------------------------|--------------|
| TSH, mIU/l | 1.53 ± 0.81 | 1.45 ± 0.68 | F= 0.472; p=0.493 | 0.4 - 3.6 |
| FT4, pmol/l | 13.60 ± 2.65 | 16.73 ± 2.23 | F= 61.45; p<0.001 | 9 - 21.07 |
| FT3, pmol/l | 4.02 ± 0.85 | 5.17 ± 0.81 | F= 68.354; p<0.001 | 3.34 - 5.14 |

TSH: Thyroid stimulating hormone; FT4: Free Thyroxine; FT3: Free Triiodothyronine; p<0.05.

Table 3: Correlations between age, thyroid axis hormone concentrations and severity of affective symptoms among hospitalized patients with high suicidal risk, n=52.

| | HAD-D score | HAD-A score | FT4, pmol/l |
|-------------|------------------------|----------------------|------------------------|
| Age, years | r = 0.313; p = 0.024 | r = 0.249; p = 0.076 | r = - 0.181; p = 0.021 |
| TSH, mIU/l | r = - 0.478; p < 0.001 | r = 0.052; p = 0.704 | r = - 0.119; p = 0.132 |
| FT4, pmol/l | r = 0.070; p = 0.609 | r = 0.137; p = 0.314 | n/a |
| FT3, pmol/l | r = - 0.120; p = 0.379 | r = 0.032; p = 0.815 | r = 0.504; p < 0.001 |
| HAD-D-score | n/a | r = 0.569; p < 0.001 | - |

HAD-D: Hospital Anxiety and Depression scale, Depression Subscale; HAD-A: Hospital Anxiety and Depression scale, Anxiety Subscale; TSH: Thyroid Stimulating Hormone; FT4: Free Thyroxine; FT3: Free Triiodothyronine; p<0.05.

and controls (36.46 ± 13.13 years old vs. 34.31 ± 12.96 years old, respectively; p=0.307), but patients' group had a lower prevalence of men (33.9.1% vs. 57.5%, respectively; p=0.003). Only 23.2% of hospitalized suicidal patients were diagnosed with a depressive disorder; about two thirds (62.5%) had a diagnosis of adjustment disorder; other patients, respectively, diagnosis of alcohol abuse.

The severity of affective (anxiety and depressive) symptoms of study subjects were analyzed. The mean score of HAD-D subscale corresponds to an asymptomatic severity of depressive symptoms and mean score of HAD-A subscale corresponds to a mild severity of anxiety symptoms.

According to suicidality, we divided all study patients into two groups - 16.1% of patients were hospitalized due to severe suicidal ideations and high risk of suicide and 83.9% were hospitalized after suicidal attempt. The relationship between suicidality groups and sociodemographic factors were analyzed. The patients were divided into three age groups, with one-third in the group. The results showed the differences between age groups: the younger patients were more likely commit suicide attempt, than older patients group ($\chi^2 = 6.835$; df = 2; p = 0.033); with no statistically significant differences in suicidality between male and female ($\chi^2 = 0.529$; df = 1; p = 0.467). There were no statistically significant differences in depressive and anxiety symptoms severity among suicidality groups.

The evaluation of thyroid function revealed that 4 patients and 6 controls had TSH concentrations higher normal range and 4 controls - lower normal range: those patients were excluded from future evaluations. So, the blood samples of 52 euthyroid suicidal patients - 18 men (34.6%) and 110 euthyroid controls - 63 men (57.3%) were used for biochemical comparisons.

The comparison of thyroid axis hormones concentrations among two groups revealed that the patients with high suicide risk in comparison to donors - controls had significantly lower mean FT3

concentrations (4.02 ± 0.85 pmol/l vs. 5.17 ± 0.81 pmol/l, respectively; p<0.001) and significantly lower mean FT4 concentrations (13.60 ± 2.65 pmol/l vs. 16.73 ± 2.23 pmol/l; p< 0.001), without significant differences in TSH concentrations (Table 2).

No statistically significant differences in thyroid axis hormone concentrations among two suicidality groups were found.

As shown in Table 3, the investigation of the associations among age, thyroid axis hormones concentrations, and severity of affective symptoms among euthyroid suicidal patients revealed some significant correlations.

The older age showed significant positive correlation with higher severity of depressive symptoms (r = 0.313, p = 0.024) and negative correlation with FT4 concentration (r = - 0.181; p=0.021). Severity of depressive symptoms significantly related us severity of anxiety symptoms (r=0.569; p<0.001). Lower concentrations of TSH related with higher severity of depressive symptoms (r= -0.478; p<0.001), but not anxiety. Thyroid hormones concentrations did not show any significant relations with affective symptoms.

Discussion

The main finding in our study is that euthyroid patients with high suicide risk in comparison to donors - controls had lower mean FT3 concentrations and lower mean FT4 concentrations, without significant differences in TSH concentrations. The similar data about differences in FT3 concentrations were found in the study by Pompili et al. in 2009. They indicated that suicidal attempters were 2.27 times less likely to have higher FT3 values than non-attempters [17]. A later study with a different clinical population in France, conducted by Diuval et al. (2010) reported that patients, who attempted suicide, had lower levels of FT4 and normal levels of FT3, while both hormone levels of patients without a history of suicide met the normal limits [18]. Those findings and the results of our prospective study indicate that lower concentrations of both - FT3 and FT4 may have the relation to suicidal behavior.

The study by Maes and colleagues in 1989 also investigated differences in thyroid hormones concentrations between patients with suicidal ideation and those without. Contrary to our findings - no significant differences were found [19]. In our study, we didn't indicates any thyroid hormones concentrations differences among two suicidality groups: patients hospitalized after a suicide attempt and patients hospitalized with severe suicidal ideations. This is probably due to a small sample size in our study and further research in this area would be useful.

In the present study, we analyzed the relationship between suicidality and age. The results showed that younger people are more likely to commit suicide attempt than older ones. The studies by Raposo and colleagues in 2014 also found that suicide ideations were more prevalent among younger adults [20]. In the study by Nicoli et al. in the French community sample of 6796 adults a significantly higher risk of suicide-related outcomes was found among younger participants [21]. So, in our study younger patients had less depressive symptoms but were at higher risk for a suicidal attempt. There are several potential explanations for such results. One possibility is that specific personality traits may be important in adaptation problems, especially during young age. According to literature results any

personality disorder, as well as any mood disorder, are named as important risk factors for self-harm by young people [22]. In a similar way, a need for attention and seeking of help from family and friends may be a reason for suicidal behavior [23]. The results of all these studies identified young people as higher risk group which could be a target for suicide prevention.

Interestingly, our study showed that most hospitalized suicidal patients were diagnosed with adjustment disorder and alcohol abuse while patients with a diagnosis of depressive disorder were only for 23.2%. The reason for this could be some contributors affecting the progress of suicide attempt. Several factors like hopelessness, impulsivity, other mental disorders, and anxiety and depressive symptoms are believed to be significant for progression from suicide ideation to suicide attempt [24].

As for our study results, alcohol abuse could be one of contributing factors for provoking suicide ideation progression to a suicide attempt. In several studies, problematic alcohol use is described to be associated with impulsive behavior [25,26], which could be the reason for the impulsive suicidal behavior. What is more, socioeconomic deprivation is thought to be an important factor for alcohol consumption outcomes. People with lower socioeconomic status are stated to have more severe consequences of alcohol drinking [27]. Suicidal behavior could be a serious type of those consequences.

At the same time, alcohol has been reported having multiple effects on the HPT axis and the functioning of the thyroid gland: direct suppression of thyroid function by cellular toxicity, indirect suppression by blunting TRH response and lowered concentrations of peripheral thyroid hormones [28]. It is also noted, that chronic stress induces a decrease in thyroid hormone levels [29,30]. In another study, the stress condition was associated with decreases in peripheral T3, T4, and TSH, but not rT3, when compared with controls [31]. And as for our study results, 62.5% were diagnosed with adjustment disorder, so alcohol as a toxin for HTP axis function with a combination of chronic stress might be serious causes of suicidal behavior, especially in younger people.

Our study results suggest that older patients experience more depressive symptoms, tend to have suicidal ideation rather than actions and FT4 concentration lower with age. One of the possible reasons may be prolonged depressive state and it is known that depression leads to different consequences such as disability, low quality of life, sleep disorders, academic failure, marital conflicts, and suicidal ideation. A study of Rossom and colleagues strengthen the statement for in their study older adults were more likely to report suicidal ideation [32]. Such results suggest that older patients are psychomotor slowed because of a long time depression and that it is apparently a reason for no willpower to perform a self-harming behavior.

Furthermore, in our study more severe depressive symptoms are related to lower TSH concentrations. The findings of relations among severity of depressive symptoms and TSH concentrations in other studies are controversial. French researchers in 2012 have found that elevated serum TSH concentration may be associated with depression severity [33]. But then, the other author states that most patients with depression have blunted TSH response to thyrotropin-releasing

hormone stimulation which results in lower TSH concentration [34]. Based on one of the early studies by Linkowski and colleagues an association of depression and increased risk of suicide was determined for patients with lower TSH concentrations [35]. Additionally, more recent studies show similar results. Duval with colleagues (2010) estimated that suicide attempters have lower TSH values compared to controls [18]. Their latest study (2017) supports the results of the previous study and indicated that decreased TSH concentration is associated with depression and suicidal behavior [36].

It is believed that lower TSH concentration is due to thyroid axis dysfunction, but the reason is the object of research and some authors suggest that the serotonin deficit and TRH dysfunction are found in patients with suicidal behavior [34]. Duval and colleagues widely discuss their hypothesis of lower TSH concentration due to chronic TRH hypersecretion in the recent study, where TRH is stated as a homeostatic modulator in central nervous system which hypersecretion is thought to be a compensatory mechanism in serotonin activity normalization and when it works effectively a decrease in serotonin function triggers an increased TRH secretion which secondarily normalizes serotonin neurotransmission [36]. In our study, no relations in TSH concentrations and suicidal behavior was found. In previously mentioned studies, serotonin deficiency is believed to be one of the main factors for suicidal behavior. As for our study results, most patients had adjustment and alcohol abuse disorders, so it suggests that serotonin concentration in our sample group was not a significant factor for TSH concentration changes.

The current study has a few limitations that must be considered. The first limitation is that it is only a prospective study with small sample size. This limited the ability to make more detailed evaluations, which might influence the results. Second, a limitation of our current sample is that there was an uneven gender split. However, there were no differences in our outcome variable based on gender, so the current findings are summarized and valid.

In conclusion, this study helped us to understand some relations between suicidal ideations, suicidal behavior, affective symptoms, patients' age and thyroid hormones. We found significantly lower FT3 and FT4 concentrations in patients with high suicidal risk, but younger patients were more likely tend to suicidal actions than older ones. The older age of suicidal patient directly related to lower FT4 concentrations, but at the same time - to more severe depressive symptoms and less suicidal actions. On the contrary, a negative relationship between severity of depressive symptoms and TSH concentrations among suicidal patients was found. However, it can be argued that TSH is more related to affective symptomatology than with suicidal behavior.

It would be of great value to observe thyroid hormone changes in future studies comprising patients with suicide risk, in order to determine neuroendocrine variability. Based on our findings, we believe that this research would greatly benefit the studies concerning suicidal patients.

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