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THE ASSOCIATION OF PINEAL GLAND VOLUME AND BODY MASS IN OBESE AND NORMAL WEIGHT INDIVIDUALS: A PILOT STUDY

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SUMMARY

Background: *In obese individuals impaired sleep and neuroendocrine alterations such as melatonin deficits are associated with circadian rhythm disruption, altered circadian clock gene expression, and bright light at night. While the relation of pineal gland volume (PGV) and melatonin levels has recently been documented in humans, surprisingly little is known about the possible interference of the PGV and the pathophysiology of obesity in humans.*

Subjects and methods*: We therefore compared the PGV of obese with non-obese individuals; both groups were matched by age and gender. Volumetric analyses were performed on the basis of 3 Tesla high resolution Magnetic Resonance Imaging (MRI).*

Results*: We found, that the PGV was significantly smaller in obese individuals than in lean controls (P=0.036). Moreover, PGV and waist-hip ratio showed a significant negative association in controls (P=0.018, r_S=-0.602) whereas no association of both variables was found in obese individuals (P=0.856, r_S=-0.051).*

Conclusions: *Thus, the current pilot investigation suggests that pineal gland function, reflected by PGV might be involved in the energy homeostasis and pathophysiological mechanisms that contribute to the development and the maintenance of obesity in humans. Moreover, our data supports the notion that the replacement of melatonin deficits might be a novel strategy in the treatment of obesity.*

Key words: *pineal gland – obesity - body mass – BMI – MPRAGE – MRI - obesity*

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INTRODUCTION

The prevalence of obesity has been rising worldwide for many years and constitutes a major health problem on a global scale (Caballero 2007). Obesity is associated with severe and cost-intensive concomitant diseases, such as cardiac-vascular diseases, and type 2 diabetes. With the exception of bariatric surgery, current obesity treatments lack sufficient long-term efficacy and are complicated by high relapse rates to previous eating habits (Tsai et al. 2005). Additionally, a growing body of research provides evidence for the association of circadian rhythm disruption, altered circadian clock gene expression, bright light at night, impaired sleep and neuroendocrine alterations such as melatonin deficits with both weight gain and obesity (reviewed in (Fonken et al. 2014)).

Melatonin is an endogenously synthesized molecule that is secreted by the pineal gland during the night in both nocturnal and diurnal mammals, and interacts with MT1 and MT2 melatonin receptors expressed in the hypothalamic SNC and other brain regions (Reiter 1991). It has been shown in animal models, that exogenous melatonin treatment reduces body mass in obese rodents. This is why some investigators speculate that pineal gland volume (PGV) and melatonin plasma concentration might be involved in the development of obesity (Terron, et al. 2013). However, little is known about the interrelationship between PGV and the pathophysiology of obesity in humans, leaving the question unanswered whether similar mechanisms, such as shown in animals, are prevalent in obese humans. Nevertheless, it has been demonstrated that the melatonin plasma concentration is linearly correlated with solid PGV in healthy subjects (Nolte et al. 2009). Additionally, Nachtigal et al. reported an association between the melatonin plasma concentration and BMI in obese women, but not in normal weight controls or obese men (Nachtigal et al. 2005). However, the reduction of melatonin plasma concentration in obese individuals might be the result of a decrease of functional pineal gland parenchyma.

Based on these results, we hypothesize that PGV might differ between individuals suffering from obesity and lean healthy controls. Thus, the purpose of this study was to conduct the first comparative high-resolution MRI volumetric analyses of the pineal gland in obese individuals, and age and sex matched non-obese participants, which were initially derived from an fMRI-study of our group investigating differences of cue-reactivity and leptin plasma concentration in obese and normal-weight subjects (Grosshans et al. 2012).

SUBJECTS AND METHODS

Subjects

The present sample was comprised of 25 obese individuals and 26 non-obese participants matched group-wise according to age and gender. Sociodemographic data and sample characteristics are given in Table 1. Inclusion and exclusion criteria are given in (Grosshans et al. 2012). The local ethics committee had approved the study and written informed consent had been obtained from all participants prior to enrolment in the study.

Procedure

MRI scans were performed using a 3 T MR scanner (MAGNETOM Trio, Siemens, Erlangen, Germany). The T1-weighted, 3-dimensional MPRAGE data set consisted of 192 sagittal sections (section thickness, 1 mm; voxel size, 1x1x1 mm; field of view, 256x256 mm^2; repetition time, 2300 milliseconds; echo time, 3.03 milliseconds; inversion time, 900 milliseconds; flip angle, 9°). All MR images were checked for artefacts affecting the image interpretation (movement artefacts, flow artefacts etc.) by an experienced consultant for Neuroradiology (I.N.) and all images were evaluated digitally using OsiriX software (www.osirix-viewer.com). PGV was measured blinded to diagnosis, by manually defining the pineal borders on transversal reconstructed sequences. The evaluation of the PGV has been described previously in (Bumb et al. 2014).

Statistical Analyses

Statistical analyses were performed using SPSS 20 (IBM Corp., Armonk, NY, USA) for Macintosh. Sociodemographic characteristics were compared using 2-sample t-tests. Volume differences were assessed by a Mann-Whitney-U test because of data non-normality (Shapiro-Wilk test). Intrarater (second analyses after 3 months) and interrater variability (a second evaluator, unaware of the results of the first evaluation, assessed ten randomly chosen datasets) of the volume measurements were compared using Spearman rank correlation. Multiple linear regression analysis (stepwise) was applied for the PGV analysis. Age, gender, BMI and waist-hip ratio related two-way interactions with the aforementioned parameter were considered as predictors.

RESULTS

All images were fully utilizable; none of the images had to be excluded due to impaired image quality. Intrarater reliability (r_S=0.9, P<0.001) and interrater reliability (r_S=0.855; P=0.002) were both satisfying. PGV in obese individuals was significantly smaller than in controls (P=0.036; Mann-Whitney-U-test) (Figure 1), ranging from 16.2 to 100.4 mm^3 (mean 49.9±25.3 mm^3) in obese individuals and from 35.7 to 164.3 mm^3 (mean 67.6±34.3 mm^3) in non-obese participants. Moreover, multiple regression analyses showed that PGV and waist-hip ratio were significantly associated in controls (P=0.018, rho=-0.602, T=-2.718) (Figure 1), while no significant associations were revealed between PGV and age, gender and BMI (P_{min}=0.413). In obese individuals, PGV and waist-hip ratio (P=0.856, r_S=-0.052) (Figure 1), as well as age (P=0.076, r_S=-0.456), and both gender and BMI (P_{min}=0.073, r_S=0.460) (Figure 1) were not associated significantly but showed strong trends.

DISCUSSION

To our knowledge, the present study is the first *in-vivo* high-resolution MRI comparison of the PGV of obese and lean subjects. We show that PGV was significantly smaller in obese individuals than in non-obese participants, which is in line with a *post-mortem* study by Torres et al. who measured the weight and volume of formalin-fixed pineal glands and found that PGV is smaller in obese than in lean individuals (Torres et al. 2003). Our explorative analysis revealed a negative correlation of PGV and the waist-hip ratio in non-obese participants, while this correlation was not present in obese individuals. In the obese group, however, we detected an inverse relationship between the PGV and the BMI. These results suggest that altered PGV may be involved in the pathophysiology of obesity. Bigger PGV might in turn lead to alterations in physiological melatonin levels and/or melatonin secretion patterns and with normal weight and body mass.

A dysfunctional interplay between pineal gland volume and melatonin levels has been also implicated in other pathological disorders including schizophrenia, mood disorder and insomnia (Bersani et al. 2002, Bumb et al. 2014, Findikli et al. 2015).

Recently, both alterations of circadian clock processes as well as suppressed peripheral melatonin levels have been associated with metabolic disorders such as obesity, insulin resistance and diabetes (Bass et al. 2010, Fonken et al. 2014, Tan et al. 2011). These associations have been thoroughly investigated in rodents. Intriguingly, the body mass of *i.e.* the Siberian hamsters (Hoffmann 1973) and of seasonally breeding rodents (Walton et al. 2011) is associated with changes in the pineal secretion pattern of melatonin. Additionally, melatonin administration reduces body mass in rats, probably by stimulating nocturnal activity (Terron et al. 2013).

Table 1. Sociodemographic parameters and characteristics of non-obese volunteers and obese individuals

	Obese individuals	Non-obese participants	*P* Value
Sex (f/m)	18/7	17/9	0.47
Age (years)	42.7±12.6	39.3±11.5	0.61
Height (m)	1.7±0.09	1.73±0.9	0.41
Weight (kg)	107.6±16.1	67.2±10.1	*<0.001*
Waist (cm)	113.3±11.9	76.5±6.7	*<0.001*
Hip (cm)	125.2±13.9	92±4.2	*<0.001*
Waist-hip ratio	0.9±0.1	0.83±0.1	*0.02*
BMI (kg/cm^2)	37.4±5.9	22.3±1.8	*<0.001*

Values are given as mean ± SD; significant *P* values are highlighted in italics

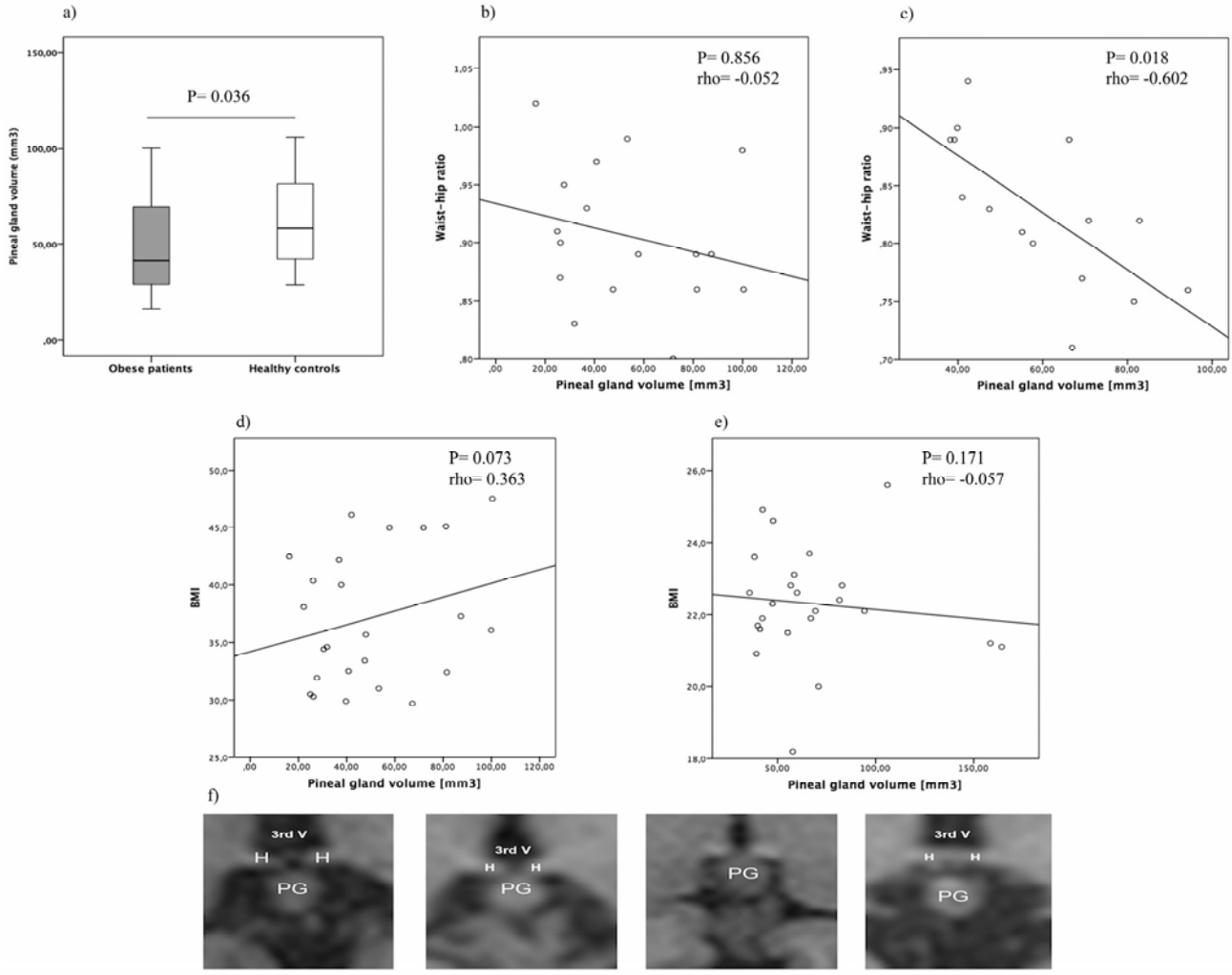

Figure 1. a) Box-Whiskers plots (box shows 5 and 95 percentiles and mean value) of pineal gland volume in obese individuals and non-obese controls (*P*=0.036, Mann-Whitney-test); Differential association of pineal gland volume and waist-hip ratio in **b)** non-obese controls and **c)** obese individuals: higher pineal gland volume was associated with lower waist-hip ratio in non-obese participants but not in obese individuals
Differential association of pineal gland volume and body mass index in **d)** obese and **e)** non-obese controls
f) MPRAGE imaging of the pineal gland demonstrating morphometric characteristics of the pineal region (PG, pineal gland; H, habenulae; 3rd V, third ventricle)

Moreover, the administration of melatonin reduces weight gain in rats fed with a high fat diet (Rios-Lugo et al. 2010) and melatonin improves glucose homeostasis in obese rats (Agil et al. 2012). The mechanism for a decrease of the body weight by melatonin in obese animals is understood insufficiently so far, and needs to be investigated further. However, Tan et al. have suggested for their Siberian hamsters model that melatonin

replacement increases the nocturnal activity of the sympathetic nervous system innervating fat tissue, thereby increasing lipolysis (Tan et al. 2011). Nevertheless, only a few translational human studies have been conducted so far. A genome-wide association study has revealed that noncoding variants in the melatonin receptor 1B are linked both to elevated fasting blood glucose and diabetes risk (Bonnefond et al. 2012). As mentioned above, Nachtigal et al. (Nachtigal et al. 2005) demonstrated that melatonin plasma concentration is associated with BMI in obese women, but not in normal weight controls (Nachtigal et al. 2005). Additionally, it has been shown that low nocturnal melatonin secretion in humans increases the risk of developing type II diabetes (McMullan et al. 2013).

A clinical open label study on the effects of melatonin on the Metabolic Syndrome (MS) has demonstrated that MS patients, besides other MS-related symptoms, had a significant higher body weight than healthy controls. In this study, melatonin given daily at a 5 mg dose for 2 months, decreased high blood pressure significantly and improved the serum lipid profile (Kozirog et al. 2011).

Due to these findings, melatonin has been suggested as a novel compound for the pharmacological treatment of the MS and obesity (Cardinali et al. 2011, Tan et al. 2011). Our results corroborate the described findings since the reduction of melatonin plasma concentration in obese individuals might be the result of a decrease of functional pineal gland parenchyma. The reason for the PGV reduction, however, remains unknown.

Apart from the small sample size, other important limitations of the investigation presented here should be mentioned. No additional CT scans or further MRI sequences were performed. Thus, our study leaves the question unanswered whether the potential role of pineal calcifications might have influenced the results of the PGV measurements and the regression analyses between PGV and nutritional variables. Therefore, it was not possible to further differentiate functional from non-functional parenchyma. Moreover, it should be kept in mind that melatonin plasma levels were not measured and, as a consequence, associations between PGV and melatonin levels could not be computed (Grosshans et al. 2012).

CONCLUSIONS

In the light of the research mentioned above and our current findings, we conclude that further investigations on this issue might contribute to the understanding of obesity and the possibility of melatonin replacement as a novel strategy in the treatment of obesity.

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