Diplomarbeit

Physical Activity and Leptin Levels in Patients with Anorexia Nervosa, Obesity, Attention Deficit Hyperactivity Disorder

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Graz, am ....

(Unterschrift)

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Graz, am …… *……*

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A huge *Thank you* to

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The staff of the children's hospital Graz

To the participating children of the children's hospital Graz

Introduction

IV. Abstracts

Deutsch

Hintergrund: Veränderungen des menschlichen Körpergewichts stehen in direktem und indirektem Zusammenhang mit energetischen Regelmechanismen. Das von den Adipozyten produzierte Hormon Leptin, spielt hier eine zentrale Rolle. Die häufig beobachtete Hypoleptinämie bei Anorexia Nervosa (AN) - Patienten kann bei schneller Gewichtszunahme in eine Hyperleptinämie und erhöhtem energetischem Verbrauch mit vermindertem Therapieerfolg führen. Bei 31-80% der AN-Patienten wird eine Hyperaktivität mit mehr oder weniger validierten Aktivitätserhebungen berichtet. Da der Leptinspiegel mit dem BMI und dem Körperfettanteil stark korreliert, findet man bei adipösen Patienten eine Hyperleptinämie, die jedoch bei Gewichtsabnahme reversibel sein. Leptin bewirkt viele Effekte auf dem menschlichen Körper. Es reguliert einerseits die Nahrungszufuhr, hat einen essentiellen Einfluss auf die physische Aktivität und vermittelt auch in anderen Organsystemen wichtige Impulse. Das Ziel der vorliegenden Studie war die Darstellung der Auswirkungen von Leptin auf die körperliche Aktivität in essgestörten Patienten und Kindern mit Attention Deficit Hyperactivity Disorder (ADHD). Weiters wurde die Bedeutung des Plasmaleptinwertes als Verlaufsparameter bei der Behandlung von Essstörungen erarbeitet. ***Methoden***: Zur Messung der körperlichen Aktivität über 72 Stunden wurden Accelerometer (ActiGraph®GT1M, Pensacola, USA) eingesetzt. Des Weiteren wurde ein Befragungsinstrument zur Ermittlung der täglichen Aktivität konzipiert. Die Körperfettmasse wurde mit dem LIPOMETER bestimmt. Serum Leptin Werte wurden im Rahmen der allgemeinen Anamnese bestimmt. ***Resultate***: Der Körperfettanteil lag zwischen 7,3% und 23,4%. Die ermittelte Schrittzahl lag zwischen 71 und 824 pro Stunde. Die Aktivität war bei AN-Patienten am höchsten. Serum Leptin Werte lagen zwischen 0,1 ng/mL und 11 ng/mL. ***Diskussion***: Die vorliegende Diplomarbeit ergibt eine umfassende wissenschaftliche Darstellung des Zusammenhangs von BMI, Körperfett, Serum Leptin Spiegel und Aktivitätsgrad bei AN, Adipositas und ADHD. Der klinische Erfahrungsbericht gibt Einblick in die Compliance und den therapeutischen Auftrag in den jeweiligen Patientenkollektiven.

English

Background: Leptin, an adipocyte derived hormone has been identified as a major factor in energy homeostasis regulation. Serum leptin levels correlate significantly with body fat mass and the BMI, suggesting low leptin levels in anorectic patients and excessive leptin values in obese patients. This observation has been made frequently. Hypoleptinemia – found in anorexia nervosa – may switch to hyperleptinemia if weight gain is reached too quickly and result in appetite suppression, thus leading to the exact opposite reaction than needed in the therapy of anorexia nervosa. Leptin also plays a major role in the regulation of physical activity – another factor in regards to energy homeostasis. Therefore, the question arises, if leptin supplementation may possibly be a therapy-option for eating disorders in the fight against hyperactivity in this patient group. On the other hand, leptin might also be useful in the therapy of obesity, due to its known function as an appetite suppressant. And finally, does leptin offer a new therapy option to us for attention deficit hyperactivity disorder (ADHD) affected children? ***Methods***: Accelerometers (ActiGraph®GT1M, Pensacola, USA) were used to measure physical activity over a period of 72 hours. Furthermore a questionnaire was developed to evaluate the daily physical activity. The body fat mass was determined using a LIPOMETER. Serum Leptin values were determined within the general anamnesis. ***Results***: The body fat percentage lay between 7.3% and 23.4%. The ascertained number of steps lay between 71 and 824 per hour. The activity was highest for the AN-patients. Serum Leptin values ranged from 0.1 ng/mL to 11 ng/mL. ***Discussion***: The presented thesis provides a comprehensive scientific presentation of the connection between BMI, body fat, serum leptin levels and the level of physical activity in AN, adipositas and ADHD. The clinical experience report gives an insight into the compliance and the therapeutic brief for the respective patient groups.

Physical Activity and Leptin Levels in Patients with Anorexia Nervosa, Obesity, Attention Deficit Hyperactivity Disorder

1. Leptin

1.1. The name, human plasma concentration and expression

Leptin, the name derived from the Greek word '*Leptos'* meaning thin, is a hormone translated and transcribed mainly in fat cells and was discovered in 1994 by Jeffrey M. Friedman et al. At a size of 16kD, this hormone plays a significant role in the regulation of body weight by inhibiting food intake and stimulating energy expenditure but also has a crucial role as a hormone cytokine in the regulation of physiological processes (Moschos et al., 2002; Baratta, 2002). This adipocyte derived protein is made up of 167 amino acids of which 146 make up the protein found in the plasma (Barrata, 2002).

Leptin concentrations range from 2 to 10 ng/mL in lean women and from 10 to 100 ng/mL in obese women and are secreted in a pulsatile manner, with maximum secretion from midnight to 7am (Baratta, 2002).

Leptin may be expressed in and secreted in a wide range of body tissue but the main source is represented in white fat cells. Circulating plasma leptin levels correspond directly with the amount of white fat tissue and adipocyte size, indicating that obesity is characterized by hyperleptinemia. A growing concern in modern society is youth obesity. A hypothesis linking adipositas and leptin is described as a resistance to or a complete lack of leptin in this group of patients resulting in an inability of leptin to reach the appetite regulating regions in the hypothalamus (Paracchini et al., 2005).

Serum leptin levels correlate significantly with body fat mass and the BMI and are not modulated acutely by a single meal ingestion. Leptin rather reacts on chronic changes in food intake behaviour (Jéquier, 2002).

1.2. Genetics

1.2.1. Leptin - LEP

The LEP gene, or Ob gene, carries the leptin encoding information. The fluorescence in situ hybridization technique was used to identify Chromosome 7 as the carrier of this adiposity linked gene. It is formed by three exons separated by two introns and mainly transcribed and translated in adipose tissue (Isse et al., 1995). It has been found that the

LEP gene is over expressed in adipose tissue in massively obese patients (Paracchini et al., 2005).

Interestingly, the genetic sequence of this leptin encoding gene is preserved in all mammalian species with a homology of over 80% (Barrata, 2002).

In 1950 mutations of the LEP gene were found for the first time in so-called ob/ob mice. These mutations, only few of which have been found in humans (Farooqi et al., 2002), resulted in severe obesity, hyperphagia, hypothermia, insulin resistance and infertility. Due to a nonsense mutation in codon 105 of the original mouse strain leptin, normally secreted by adipocytes, is not produced and can therefore not fulfil its food intake and energy expenditure regulating functions (Paracchini et al., 2005).

Though a mutation in codon 105 could not be found in humans, an alteration of the LEP gene in codon 133 in humans, described by a deletion of a single guanine nucleotide, was reported in two children with the same consanguineous pedigree. This resulted in very low leptin serum levels despite early onset obesity and thus further underlines the thesis that leptin plays a significant role in appetite and energy expenditure regulation (Montague et al., 1997).

1.2.2. Leptin receptors - LEPR

The receptor encoding gene is found in humans on chromosome 1. Six splice variants of the leptin receptor (Ob-R) have been identified (Aparacio et al., 2005; Paracchini et al., 2005). One differentiates between long (LEPRl) and short forms (LEPRs) of the receptor, differences are found only in the length of cytoplasmic domains. The extracellular and transmembrane domains are identical. Another form of receptor, the soluble form (LEPRe), exists entirely of extracellular domains, thus having no intracellular motifs. It is known that leptin interacts with these receptor isoforms in the brain, the male and female reproductive organs, the mammary gland, the gut, the kidney, the lung and, with leptin having many structural similarities to other cytokines, the immune system (Paracchini et al., 2005; Barrata, 2002).

The most important isoforms, the long form of the leptin receptor (also described as Ob-Rb), is predominantly found in the hypothalamus. This 120 kDa receptor mediates the leptin actions through the involvement of the phospatidylinositol 3 kinase and the Janus

kinase/STAT3 – signalling pathway. Other organs seem to be missing this form. On the other hand, the shorter forms are expressed in the entire body, especially in the kidneys, lungs and choroid plexus (Paracchini et al., 2005).

1.3. Mode of action:

1.3.1. Leptin interacting with receptors

Leptin targets so-called long forms of the leptin receptors (LRb, OB-Rb) in the hypothalamus which then mediate important leptin actions over the STAT3-signaling pathway. The OB-Rb is one of five different isoforms (Burguera et al., 2000).

To access these receptors, leptin passes the blood-brain barrier via a specific transport system. Furthermore hypothalamic arcuate nucleus neurons sense leptin independently of this transport system by having direct contact to the circulation (Faouzi M. et al., 2007).

1.3.2. The STAT3 Signaling Pathway

Cytokines activate the cell surface tyrosine kinases cytokine receptor (Ob-Rb) and trigger the response of the *Signal Transducers and Activators of Transcription (STATs) pathway.* A major role in this pathway lies in the so called JAK-kinases (Janus-kinase). When cytokines bind to the surface receptors the activation of JAKs is triggered, whereby tyrosine residues on the receptors are phosphorylated and create sites for interaction with proteins containing SH2 domains, which bind to the now phosphorylated tyrosine. STATs possess the necessary SH2 domains to bind the phosphotyrosine residues and are recruited to the receptors. After binding to the receptor, the JAKs then phosphorylate the STATs hereby creating new docking sites for SH2 domains on other STATs, inducing their dimerisation. An accumulation of activated STAT-dimers in the cell nucleus trigger transcription of their target genes (Hebenstreit. et al., 2005).

Fat cells, adipocytes, release the hormone into the bloodstream where it then interacts with the hypothalamus, which analyses the amount of circulating Leptin. In the striatal regions, Leptin is found to modulate neuronal activation, regulating food intake by reducing the perception of food reward while generating a higher response to satiety signals during food consumption (Farooqi et al., 2007).

1.4. Sites of action

Leptin interacts with leptin receptor isoforms in the brain, the bones, the male and female reproductive organs, the mammary gland, the gut, the kidney, the lung and, with leptin having many structural similarities to other cytokines, the immune system.

1.4.1. Hypothalamus

One of leptin's main sites of action lies in the hypothalamus. Here the basomedial region - including the arcuate nucleus - plays a significant role in interactions between the CNS and this hormone. The result of leptin activating receptors in the hypothalamus is the release of anorexic peptides on the one hand and the suppression of orexigenic peptides on the other, resulting in an overall decrease in caloric intake (Leshan et al., 2006).

As already mentioned, the arcuate nucleus (ARC) is one of the main regions involved in the food intake and satiety processes. The hypothalamic arcuate nucleus neurons sense leptin by means of direct contact to the circulation (Faouzi M. et al., 2007). Here neurons produce and secrete several neuropeptides, including neuropeptide Y (NPY), agouti-related peptide (AgRP) and the melanocortin precursor pro-opiomelanocortin (POMC), which shall be further described in more detail below.

Leptin reaches these neurons through the blood-brain barrier, which is modified specially to allow leptin and insulin, two important hormones concerning energy homeostasis, to enter the brain and interact with the hypothalamus neurons (Arora et al., 2006).

Found in the superior part of the third ventricle in the anterior hypothalamus the paraventricular nucleus (PVN) is a junction point of neuronal projections from the ARC. As the PVN is the main site of corticotrophin-releasing hormone (CRH) – also known as Corticoliberin - and thyrotropin-releasing hormone (TRH) secretion it is evident that this region plays a role in the integration of nutritional signals with the thyroid and hypothalamic-pituitary-adrenal -axis (HPA axis) (Neary et al., 2004).

1.4.2. Pituitary gland

Situated in the pituitary fossa just below the optic chiasma the pituitary gland secretes trophic hormones involved in actions mediated by leptin. The main focus concerning the involvement of leptin with the pituitary gland lies on the anterior lobe, the adenohypophysis. In an in vitro study by Yu et al (1997), several hormones secreted by the

small gland were tested for their response to leptin. Luteinizing hormone (LH) levels were significantly raised by leptin, showing a similar reaction of the pituitary gland to leptin as to the luteinizing-hormone-releasing-hormone (LHRH or gonadotropin-releasing-hormone 1, GNRH1). In addition, the release of the follicle stimulating hormone (FSH) after leptin stimulation emphasizes the influence of the adipocyte secreted hormone on the hypophysis' anterior lobe The results of this study suggest that leptin shows only a slightly lower effectiveness in releasing the hormones LH and FSH from the pituitary gland than LHRH does (YU et al., 1997).

Patients with low serum leptin levels could show, as a result of inadequate secretion of LH and FSH, signs of secondary amenorrhoea and temporary infertility (Montez et al., 2005).

1.4.3. The pancreas

An increasing concern in modern society is without a doubt the rising prevalence of obesity in general and especially in childhood. A connection between this increase and the more often diagnosed type II diabetes can clearly be made (de Ferranti et al., 2007). Therefore a closer look at one of the main characters in the pathogenesis of type II diabetes, the pancreas and specially the insulin secreting pancreatic ß-cells, must be taken.

Of all the known six isoforms, the long leptin receptor isoform (ObRb) is currently believed to be the most important form in fulfilling the physiological tasks of leptin. Linking the long isoform to the ß-cells of the pancreatic islets was made by interpreting the outcome of experiments performed on db/db mice, which have a genetic defect resulting in an isolated absence of only one isoform, namely the long isoform, ObRb. The phenotype of this strain of mice had a very close resemblance to ob/ob mice, which are leptin deficient and also show hyperinsulinaemia. These results suggest that the leptin effect on the ß-cells is mediated by ObRb (Kieffer et al., 2000).

The ß-cells are not the only targets of leptin in the pancreas. According to Shallu et al (2007), leptin decreases cholecystokinin (CCK) – induces amylase secretion from the acinar cells and augments the CCK-mediated intracellular calcium release. These results were found in rats, but an effect on the exocrine function of the human pancreas should also be considered (Shallu et al., 2007). But it must also be said, that different studies do show varying results. It was shown that a high leptin dose could, in contrast to the

previously mentioned, in fact increase the secretion of pancreatic enzymes. These results were obtained in animal experiments only. An effect of leptin on the human exocrine pancreas is yet to be proven (Midha et al., 2007).

Unlike the exocrine reaction of the pancreas to leptin in humans, the effect of leptin on the ß-cells has been demonstrated in various human studies, indicating an association between insulin and leptin resulting furthermore in a connection between leptin and the pathogenesis of diabetes (Niswender et al., 2007).

An interesting approach to this relationship between leptin and the pancreas lies in the hypothesis of an adipo-insular axis (Kieffer et al., 2000). As mentioned, pancreatic beta-cells are equipped with the long form of leptin receptors ObRb, giving leptin, independently of the central nervous system, an important role in the regulation of energy homeostasis. The background of this postulated hypothesis is that in leptin deficient or leptin resistant mice, hyperinsulinemia proceeded the development of obesity and diabetes. Interestingly these ob/ob mice reacted with a decrease of plasma insulin levels after the administration of exogenous leptin of 75% in 24 hours (Seufert et al., 1999).

Despite the influence on insulin secretion, leptin couldn't be linked to the development of either type 2 diabetes or pancreatic diabetes (Midha et al., 2007).

Leptin can inhibit the pancreatic ß-cell secreting insulin by keeping the membrane-bound K-atp-channel open and thereby hyperpolarizing the ß-cell plasma membrane resulting in attenuation of the voltage gated Ca^{2+}-channel or by a cut off of insulin secretion (Niswender et al., 2007).

1.4.4. Cardiovascular system

Obesity has become one of the most important medical issues in industrial countries and is associated with increased cardiovascular mortality and morbidity. Although, on a molecular basis the direct connection between obesity and cardiovascular diseases has not been identified yet, a possible explanation could lie in the involvement of leptin in regulating vascular tone (Fortuño A et al., 2003).

1.4.5. Male and female reproductive organs

Leptin receptors were found to be located on germ cells and on Leydig-cells within the testis, suggesting that leptin may have a regulatory influence on the male reproductive system. In Ob/Ob mice, spermatogenesis is reduced and apoptosis in the testes dominates, thus reducing the level of proliferation of early germ cells. As a result hypogonadism can be observed. An estimated 75% of all potentially mature spermatozoa are affected by the apoptosis. The administration of leptin in leptin deficient mice was able to restore the function of spermatogenesis and reproductive function (Bhat et al., 2006).

Estrogens induce whereas androgens suppress leptin production, providing an explanation for the sexual dimorphism in serum leptin levels (Moschos et al., 2002).

On the level of the hypothalamic-pituitary-gonadal axis (HPG-axis), leptin stimulates the secretion of the gonadotropin-releasing hormone (GnRH). Ob-Rb receptors are found in the hypothalamus, mainly in the arcuate and ventromedial areas, responsible not only for food intake but also for sexual behaviour. This is thought to be an indirect effect of leptin, acting via several interneurons. Furthermore, leptin induces the secretion of LH and FSH from the pituitary gland (Moschos et al., 2002).

Leptin receptors were detected on ovarian cells, including granulosa, theca, and interstitial cells. High leptin levels (>10ng/ml) seem to antagonize the effect of several growth hormones on the steroid synthesis, thus leading to low estradiol levels. This effect (reduced steroid synthesis) was also observed in Leydig cells resulting in a decreased testosterone serum level (Moschos et al., 2002).

During menstruation Ob-Rb levels in the endometrium rise consistently up to a peak level during the secretory phase. During pregnancy, and especially in the first trimester, Ob-mRNA is found in abundant concentration in the chorionic villi. The mother's serum leptin levels also rise considerably during this time (Masuzaki et al., 1997). Moschos et al (2002) furthermore describe a connection between Ob-Rb deficiency and endometrium maturation defects and subfertility (Moschos et al., 2002).

In the myometrium no significant Ob mRNA could be found (Masuzaki et al., 1997).

1.4.6. Mammary gland

Leptin and its receptors have been found in the mammary gland of humans as well as other species and the amount of leptin expressed during pregnancy varies, highest concentrations found especially during the first half of pregnancy. Furthermore, leptin could play an important role in the development and function of the mammary gland, as findings of the effect of leptin on milk protein expression and lactation as well as findings of leptin in human milk and its effects on the mammary epithelium differentiation have been reported (Baratta, 2002; Moschos et al., 2002).

1.4.7. Bone

Osteoporosis, among other things the result of gonadal failure, can be prevented by obesity. Although this mechanism is not quite understood, it suggests a common connection between bone mass, body weight and gonadal function (Ducy et al., 2000).

An indication for the presence of such connection - a general implication of leptin on the formation of bone mass - can be interpreted from the findings of Ob-Rb receptors in primary osteoblasts and that leptin has been shown to enhance the differentiation of multipotent bone marrow stromal cells into osteoblasts (Moschos et al., 2002). However, it should be mentioned that in 2000 no such receptors were found in an examination performed by Ducy and colleagues (Ducy et al., 2000).

A different stimulating effect of leptin on the osteoblast function, this time via the hypothalamus, was observed in a study conducted by Ducy et al. in 2000, suggesting that leptin doesn't directly stimulate the osteoblasts (Ducy et al., 2000).

In ob/ob mice (leptin deficient mice) one would expect a significant bone mass loss due to the previously described hypogonadism which leads to an increase of the osteoclast number (Ducy et al., 2000) and hypercortisolism (Dagogo-Jack et al., 2005; Ducy et al., 2000), both states shifting the balance between bone resorption and bone formation towards enhanced resorption. Nevertheless, leptin deficient ob/ob mice and db/db mice (obese and diabetic mice (Sahai et al., 2004).) showed an increase of trabecular bone mass by an approximate 2-fold compared to wild-type mice but without effecting cortical bone mass. To identify leptin as the mediator of this effect, Ducy and colleagues (2000) conducted several observations in other mouse-models, such as the so called Agouti yellow

mouse and other obese but not leptin deficient mice. The findings of normal bone mass in these mouse models seem to prove the hypothesis of an involvement of leptin in bone formation. There seems to be discrepancy in the views taken on the mode of action of leptin in regards to bone-formation (Ducy et al., 2000).

The osteoclastic function is not suppressed by leptin deficiency and thus does not contribute to the increase of bone mass (Ducy et al., 2000).

1.4.8. The gastrointestinal tract

In 2005 a scientific group detected leptin as early as in the fetal stage of human life. These foetuses, 29 in all, were obtained after voluntary, spontaneous, or therapeutic abortions. Immunohistochemical procedures to identify and highlight the human long form of leptin receptors in bouin-, formalin, or paraformaldehyde-fixed fragments of the fetal gastrointestinal tract were used to obtain the results. From about the 15th week of gestation, leptin signals were mainly found to be located on basal membranes of surface epithelial cells and parietal cells. Another method used to find evidence of leptin receptors was the RT-PCR. This showed a 120kD protein band in the stomach, small intestine, and colon of foetuses as in adult gastrointestinal tract. In summary, leptin was found in the oesophagus, the stomach, the small and large intestine of these 29 fetuses. In humans, the leptin receptor isoform Ob-Rb has been found in the fundic mucosa here especially on the apical membranes of enterocytes and colonocytes of the small and large intestine (Aparicio et al., 2005).

1.4.9. The kidney and blood pressure

The kidneys have a small amount of the full length Ob-Rb receptor, but it is unclear to what extent these receptors are responsible for the leptin effects on the kidney (Baratta, 2002).

Obesity is associated with several co-morbidities among which hypertension is frequently observed. The influence of leptin on blood pressure is thought to lie in two mechanisms (Bravo et al., 2006):

a) An increase of renal sympathetic nerval activation (RSNA) (Haynes et al., 1997)

b) The synthesis and release of nitric oxide (NO) (Beltowski et al., 2002)

An increase in blood pressure must be expected with RSNA and a decrease of blood pressure should be observed through the effect of NO.

Yet one must differentiate between the acute and chronic effects of leptin on kidney and blood pressure regulation. Despite the natriuretic and diuretic effect of acutely administered leptin, neither blood pressure nor the glomerular filtration rate is altered (Bravo et al., 2006). The decreased sodium excretion is explained by Beltowski et al (Beltowski et al., 2002) due to a reduced activity of the sodium-potassium exchanger (Na/K-ATPase) in the renal tubule. The steady state of blood pressure in the case of acutely administered leptin is maintained by a systemic release of NO, an increase in NO production in endothelial cells and blood vessels and the natriuretic and diuretic effect opposing the effect of the RSNA (Vecchione et al., 2002).

An interesting hypothesis mentioned in a review by Bravo and colleagues (2006) suggests a peripheral leptin resistance in obese rats, probably due to a down-regulation of peripheral leptin receptors, as these rats showed no natriuresis in the state of an acutely high leptin infusion (Bravo et al., 2006).

Conversely, the chronic effect of leptin leads to an increase of both RSNA and blood pressure probably due to a reduced natriuresis by up-regulation of the Na/K-ATPase. High leptin levels may lead to NO deficiency, as it is believed that obesity causes a high level of systemic and intrarenal oxidative stress. As a result, the blood flow to the kidneys is reduced by up to 30%, thus leading to a decreased natriuresis and high blood pressure (Bravo et al., 2006).

1.4.10. The lungs

One suspects leptin to act as a growth factor in the lungs and as a modulator of central respiratory control mechanisms. Therefore the hypothesis is that in obesity, leptin resistance could be one reason for breathing problems in this patient group. Leptin has also been positively linked to surfactant production (Baratta, 2002).

1.4.11. Immune system

Although energy reserves are necessary for a good functioning of the immune system, obesity has a negative influence on the immune system. Several links of leptin with the immune system are evident. For example, leptin presents a structure similar to that of cytokines, especially the IL-6 family. Furthermore, it has been identified that leptin serves as a survival signal for CD4+CD8+ T lymphocytes and it normalized the absolute number of naive CD4+CD45RA+ lymphocytes after administration of recombinant human leptin in leptin deficient children. Linking leptin to the functioning of the immune system in diet induced, obese patients can be made through the observation of lymphopenia and their suppressed proliferative response. These characteristic traits are reversible when food intake is restricted, thus decreasing leptin levels. Furthermore, leptin levels also correlate with serum TNF-alpha levels, which lead to a suppression of lymphocytes (Matarese et al., 2005).

1.4.12. The sympathetic nervous system

The sympathetic system seems to contribute to the level of circulating leptin as it is known -in vivo - to be a key regulator of lipolysis. One suspects the involvement of the SNS in serum leptin levels to lie in an inhibitory effect on the ob gene transcription. To prove this theory, a study was performed in which propranolol, a ß-adrenoreceptor antagonist, was administered and showed attenuation in the fasting-induced reduction in circulating leptin. In a human patient with a removed phaeochromocytoma, low levels of circulating noradrenaline and adrenaline was accompanied by a significantly increased serum leptin level (Trayhurn et al., 1999).

1.5. Leptin during pregnancy

During pregnancy, hyperleptinemia is most particularly observed in the first half of pregnancy, with leptin levels dropping drastically after birth. Furthermore, leptin resistance could be present, as pregnancy implies a state of increased energy intake, which is not the effect expected to occur in hyperleptinemia (Moschos et al., 2002).

2. Neuropeptides controlling appetite

The regulation of appetite, food intake and thus energy homeostasis is mainly conducted in the hypothalamus and its conjoining regions, like the arcuate nucleus (Kalra et al., 1999). Influencing these regions are peptides, produced in the periphery such as the stomach, adipose tissue or the pancreas. One differentiates between anorectic and orexigenic peptides, resulting in a decrease of caloric intake and an increase of appetite, respectively (Arora, 2006).

2.1. Peripheral hormones regulating appetite

2.1.1. Insulin

Insulin, first detected 1869 by the German medical student Paul Langerhans, is a protein consisting of 51 amino acids, 21 of which belonging to the so called A-chain and 30 to the B-chain. These two chains are connected to each other by two disulphide bonds. A third disulphide bond lies on the A-chain. The C-peptide, lying in between the A and B chain is split off and released into the blood together with the active insulin, now consisting only of the disulphide connected A and B chain (Horn et al., 2002)

This hormone, synthesized in the pancreatic beta cells of Langerhans-islets, regulates appetite through serum glucose levels. Glucose, besides being a nutrient, cooperates with insulin and leptin in the hypothalamus in coordinating the melanocortin-pathway, which suppresses appetite and reduces food intake (Neary et al., 2003). Further details on the melanocortin pathway can be found below. Receptor mediated transport allows insulin to pass the blood brain barrier and reach the hypothalamus, where it then causes a reduction in food intake (Baura et al., 1993).

Food intake, resulting in an increase of serum glucose levels, causes a rise of circulating insulin. This rise of insulin is proportional to body fat mass, but interestingly patients with type II diabetes, often found in what is known as the metabolic syndrome, do not react as expected with a reduction of caloric intake but rather with a gaining of weight. This is explained by the lipogenic effects of insulin and the loss of the anorexigenic effect of hyperglycaemia in this group of patients (Neary et al., 2003).

2.1.2. Leptin

Secreted mainly from the adipose tissue, leptin serum levels are directly proportional to adiposity in humans. Leptin plays a major role in energy homeostasis, the association between obesity, hyperphagia and leptin deficiency has been demonstrated (Farooqi et al., 2002).

Main site of action concerning food intake is the hypothalamus.

2.2. Gastrointestinal peptides

2.2.1. Ghrelin

Ghrelin, a small 28 amino acid peptide produced mainly in the stomach is an endogenous orexigenic peptide as it stimulates appetite and increases food intake. Ghrelin differs from other orexigenic peptides in the fact that it seems to be the only peptide hormone to additionally stimulate appetite when administered peripherally when others only function, when injected centrally. Food intake is a key regulator of plasma ghrelin levels. The plasma ghrelin levels respond to an increase of glycaemia by decreasing and by increasing when serum glucose levels sink (Wren et al., 2000).

In meal initiation ghrelin also plays an important role, as it rises significantly before meals. In the hypothalamus ghrelin stimulates neurons expressing NPY and agouti-related peptide (AgRP) in the arcuate nucleus and orexins from lateral hypothalamic regions, all leading to an increase in appetite and food intake (Korbonits et al., 2004).

Ghrelin stimulates GH by acting as an endogenous ligand for the growth hormone secretagogue receptor (GHS-R) (Neary et al., 2003) and thereby stimulates appetite, increases fat mass deposition thus resulting in a gain in bodyweight. GH secretion is strongly influenced by ghrelin serum levels and shows a synergetic effect with the growth hormone releasing hormone GHRH (De Vriese et al., 2007).

Energy homeostasis is maintained by ghrelin in such a way that, in anorectic patients, it stimulates food intake, decreases energy expenditure, decreases the utilization of fats and increases utilization of carbohydrates. In obese patients it leads to the exact opposite. But, as demonstrated with ghrelin-null mice, which are physiologically and pathologically

indistinguishable from normal mice, energy homeostasis must underlie several other mechanisms apart from ghrelin (Klok et al., 2007).

2.2.2. Peptide YY (PYY)

Secreted from the L cells of the small and large bowel after food ingestion in proportion to the calorific content of a meal, the main form of PPY - PYY 3-36 - leads to an inhibition of food intake (Neary et al., 2003; Batterham et al., 2002).

PYY is a member of the neuropeptide Y (NPY) family and interacts as an agonist with Y2 receptors located in the hypothalamus. It could be shown that an infusion of PYY in physiological, postprandial concentrations in humans could reduce food intake by over 30% in 24 hours (Batterham et al., 2002).

Peripheral administration of PYY 3-36 furthermore decreases hypothalamic NPY mRNA (Neary et al., 2003).

Despite the fact that PYY decreases appetite and food intake, weight loss as a result of PYY-effect is, however controversially discussed (le Roux et al., 2007).

2.2.3. Glucagon-like-peptide-1

Found throughout the entire gastro-intestinal tract, but mainly in the distal segments of the ileum and the colon, GLP-1 is considered being an incretin and releasing insulin from pancreatic ß-cells in response to caloric ingestion (Carel W. le Roux et al., 2007).

Vagal afferents from the gastrointestinal tract lead to areas of the brain controlling food intake and which react to GLP-1. This was shown in rat brains where an intracerebroventricular injection also inhibited food intake. In addition, GLP-1 administered centrally suppressed the intake of water. The importance of GLP-1 in the regulation of food intake was furthermore demonstrated with exendin amide (EA), a GLP-1 receptor antagonist. Rats treated with EA gained weight significantly in the time of administration (E. Näslund et al., 1999).

2.2.4. Cholecystokinin (CCK)

Cholecystokinin, also known as pancreozymin, is produced and secreted in the duodenum and jejunum. CCK stimulates the secretion of pancreatic enzymes and induces contractions

of the gallbladder. CCK inhibits further food intake by mediating satiety, an effect which is potentiated by leptin (Neary et al., 2003).

2.3. Orexigenic hypothalamic neuropeptides

2.3.1. Neuropeptide Y - NPY

This is a very essential hormone in the process of energy homeostasis and is classified as a member of the pancreatic peptide (PP) – family (Kalra et al., 1999). The secretion of Neuropeptide Y leads to a series of actions including an increased caloric intake, reduced physical activity and an increase of the parasympathetic tonus (Silbernagel et al., 2003)

This small, 36 amino acid containing neuropeptide is one of the most potent orexigenic agents known, shown that it acutely but over a relatively short-lived period of time stimulates feeding in rodents after a single ICV injection. Continuously high levels of NPY result in a sustained hyperphagia. A central role in meal initiation is considered one of the key effects of NPY as it maintains high levels in the PVN as long as food is withheld. Neuropeptide Y serum levels are influenced by leptin and insulin whereby the secretion from the neurons is inhibited (Kalra et al., 1999, Nakazato et al., 2001).

NPY regulates food intake dose dependently and mainly through activation of Y1 and Y5 receptors. Out of several sites in the brain in which NPY is produced and secreted, two have been identified as the main sources of NPY, these being the brainstem on the one hand, and the hypothalamus along the length of the arcuate nucleus and the dorsomedial nucleus, on the other. In the brainstem other hormones such as the catecholamines, norepinephrine and epinephrine, and galanin are coproduced with NPY. Experiments have shown that practically all the norepinephrine and epinephrine found in the hypothalamus comes from the neurons situated in the brainstem (Kalra et al., 1999).

2.3.2. Orexin

Two types of orexins are know, type A and type B and both perform their orexigenic effect via G-protein coupled receptors in the dorsal and the lateral hypothalamus as well as in the perifornical hypothalamus. The mechanism of increased food intake is thought to be a

delay in the onset of satiety signals (Arora et al., 2006), however in the stimulation of food intake, orexins are not as potent as NPY (Kalra et al., 1999).

2.3.3. Agouti-related-protein (AgRP)

The AgRP antagonizes the suppressing effect of the alpha-melanocyte-stimulating hormone on food intake at the MC3 and MC4 receptors and therefore enhances food intake. The effect on the arcuate nucleus is long lasting, in animal studies a single central injection of AgRP resulted in hyperphagia for an entire week. AgRP is co-secreted with NPY and norepinephrine (Taylor et al., 2006) and the AgRP neurons are inhibited by leptin (Neary et al., 2003).

2.4. Anorectic hypothalamic neuropeptides

2.4.1. The melanocortins

The precursor molecule for the melanocortins is proopiomelanocortin (POMC) which is tissue specifically cleavaged. The main character in this category of appetite regulators is the alpha-MSH (melanocortin-stimulating hormone), which is derived from POMC in the brain (Neary et al., 2004). Besides being a precursor molecule for alpha-MSH, numerous hormones derive from POMC such as ACTH, beta-MSH, alpha-, beta-, gamma-endorphine, beta-lipotropine, and met-enkephalin. In the pituitary pars intermedia proteases cleavage POMC into pro-MSH which is then converted into alpha-MSH (de Gruyter (Ed.), 2002)

The brain is fitted with two melanocortin receptors (MC), of which five exist in total. MC3 and MC4 were identified as the predominant isoforms, a lot of which found in the hypothalamus. So far only MC4 could be identified as the receptor promoting the effects of alpha-MSH on the restriction on food intake, thus acting anorexigenic (Kalra et al., 1999). The importance of MC4 in regulation of body weight was demonstrated in MC4-knockout mice, which showed hyperphagia, thus leading to obesity (Huszar et al., 1997).

MC4 interacts with the melanocortin 4 receptor, a G-protein-linked receptor widely found in the central nervous system (Li et al., 2008).

Endogenous agonist on the MC3 and MC4 – receptors are the melanocortins and their counterpart, the endogenous antagonist, is the agouti related protein. This results in a dynamic in vivo system in which alpha-MSH and AgRP act together (Valli-Jaakola et al., 2004).

2.4.2. Serotonin

Serotonin is a member of the monoamine system, which also includes norepinephrine and dopamine (Kaye et al., 2007). Serotonin can be found in the entire central nervous system, highest concentrations though are found in the brainstem-situated raphe nuclei (Arora et al., 2006). Monoamine neuron cell bodies project to cortical, striatal limbic regions and the hypothalamus, which contain 5-HT receptor subtypes in high density (Kaye W. et al., 2007; Neary et al., 2004).
One of these receptor subtypes, the 5-HT^{2C} receptor, was identified to show the strongest inhibition of caloric intake, demonstrated with 5-HT^{2C} knockout mice, which turned out to be hyperphagic and obese. Interestingly however, a $5HT^{2C}$ antagonist was not able to reproduce the phenotype of the knockout mice (Tecott et al., 1995).´

Besides being responsible for a potent ability to inhibit food intake and thereby reducing body weight, serotonin is involved in a wide spectrum of behavioral, psychological, and physiological processes (Lam et al., 2008).

Looking at anorexia nervosa and bulimia nervosa, serotonin contributes to dysregulation of appetite, mood, and impulse control. These attributes persist even after recovery of these patients (Kaye, 2007).

3. Anorexia nervosa and bulimia nervosa

3.1. Introduction

In adolescence the body undergoes many changes of which the most obvious are in weight and thus effect eating behaviour. During this time girls on average gain about 14kg and boys 15kg, nearly half of the young women try dieting (40%) and a quarter of the boys do equally so. It's important to recognise potentially harmful eating behaviours, because these – dieting for instance –could possibly lead to more serious eating problems (Nicholls et al., 2005).

3.2. Anorexia nervosa and Bulimia nervosa

The aetiology of anorexia nervosa and bulimia nervosa is hitherto unknown and subject of research. These dysregulations of eating behaviour occur mostly in young women and are considered to be chronic psychiatric disorders, characterised by an abnormal perspective of body weight and shape (Kaye, 2007) and are furthermore regarded as difficult to treat (Zandian et al., 2007).

Anorexia nervosa and bulimia nervosa focus on some shared diagnostically significant points such as eating behaviour and body image distortions, but also differ characteristically from each other. For example, increasing cachexia, an unmistakable sign of anorexia nervosa, results from an inexplicable fear of weight gain and an obsession with fatness, whereas having an abnormally low body weight can exclude patients from the very diagnosis of bulimia nervosa. However, it has been found that in 25% to 30% of cases, bulimics also have a history of anorexia nervosa (Kaye, 2007).

A major psychological feature of anorexia nervosa, the most lethal psychiatric disorder, difficult to treat and often attached to prolonged periods of illness is the extreme overvaluation of body shape and weight. The objective in the characteristic behaviour of anorectic patients is to burn as many calories as possible, reaching their goal by using over-exercise and over-activity, standing instead of sitting and doing sports in all variations (Morris et al., 2007).

Another important factor in relation to anorexia nervosa and bulimia nervosa can be found in the occurrence of obsessive compulsive disorder (OCD). 35% of patients diagnosed with

AN also suffered from OCD, which could be found in 7% of these patients prior to the onset of AN. But no evidence supporting the theory of OCD causing AN has so far been found (Zandian et al., 2007). Activities categorised as OCD are, for instance, repeated weighing, measuring and mirror gazing (Morris et al., 2007).

3.3. Epidemiology and aetiology of Anorexia and bulimia nervosa

3.3.1. Epidemiology

Many studies involving the incidence and prevalence of eating disorders have been conducted, coming up with very diverse results. In regards to anorexia nervosa these controversies date as far back as the 19th century (Hay et al., 2008). Meanwhile, studies have revealed a prevalence of about 1% for bulimia nervosa in young western women, while anorexia nervosa is supposed to be found in 0.3% - 0.5% of this group (Hoek et al., 2003). Other, not further specified eating disorders occur in between 2 and 5%. Hay et al (2003) were able to show in their examination that over the period of ten years (1995 – 2005) the prevalence of anorectic eating disorders, binge eating and purging have increased from 1.6% to 4.6%, 3.2% to 7.2%, and 0.7% to 1.5%, respectively. Interestingly the rise in prevalence also affected male participants to the same extent as the participants in the female group. Before puberty eating disorders occur equally in boys and girls, but thereafter in early adolescence girls are affected approximately 10 times more often than boys. The ratio then rises during young adulthood to about 1:20 (Gonzalez et al., 2007). Reviewing the results from 2005 shows that the absolute prevalence of binge eating, purging and strict dieting or fasting has increased more than a two-fold.

	1995 (n=3001)	2005 (n=3047)	p-value
Binge eating	96 (3.1%)	205 (7.2%)	<0.001
Purging	24 (0.7%)	54 (1.5%)	=0.003
Strict dieting or fasting	48 (1.6%)	129 (4.6%)	<0.001

Table 1. Prevalence increase over period of 10 years (Table modified from Hay et al., 2008).

Most commonly know is the fact that eating disorders occur predominantly in adolescence or young adulthood in females. A reason for this can possibly be found in the profound changes in several areas of the life of this population group during puberty, including biological, psychological and sociocultural changes (Kaye, 2007).

Mostly, in about 80% to 90% of cases, these disorders are found in young, adolescent woman with an average age of onset of 15 years (Morris et al., 2007). It is very interesting to see, that the age distribution of the different kind of eating disorders concerning weight controlling behavioural patterns has shifted slightly. Binge eating has gone from affecting the ages 25 to 34 in the most part to the younger group of 15 to 24 year olds (Hay et al., 2008).

But one must bear in mind that anorexia nervosa and bulimia nervosa are not specifically linked to puberty and adolescence. As a matter of fact, the range of ages affected lies, as already mentioned, between the 15 year old teenagers representing the average age of onset, and the elderly over 65 indicating that older people also suffer from eating disorders. In fact, women between the ages of 45 and 64 years appear to represent a part of the population especially preoccupied with nourishment issues. According to Hay (Hay et al., 2008), among the 3047 participants of an analysis of eating disorder behaviours in 2005, participants with binge eating behaviour were on average 2 years older than in 1995, participants with the signs of purging such as the use of laxatives, diuretics or self induced vomiting, were about 9.5 years older than in the previous survey, and participants reporting to be strictly dieting or fasting showed an increase in the mean age of nearly 11 years. This raises the average ages for the three behaviours respectively to 36.4, 48 and 38.6 years old. A possible explanation for this increase could lie in the fact that population is generally getting older (Hay et al., 2007).

	Binge eating		Purging		Strict dieting or fasting	
Age (years)	1995	2005	1995	2005	1995	2005
15-24	21.9%	29.3%	19.8%	13.6%	45.2%	20.0%
25-34	34.4%	21.3%	13.5%	9.0%	29.2%	26.5%
35-44	21.7%	18.4%	43.9%	21.2%	15.2%	17.1%
45-54	18.0%	17.4%	11.0%	28.6%	8.7%	21.4%
55-64	1.7%	7.4%	6.7%	7.5%	0%	9.7%
>=65	2.3%	6.2%	5.2%	20.1%	1.7%	5.3%
Mean (SD)	34 (13.1)	36.4 (19.8)	38.5 (14.6)	48.0 (21.7)	27.9 (10.7)	38.6 (19.8)

Table 2. Increase of mean age in eating disorders (Table modified from Hay et al., 2008).

3.3.2. Aetiology

Unlike many other disorders with clearly identified causes, the cause of AN, or eating disorders in general, cannot be easily explained through definite points. There is no doubt that social pressure and cultural demands present a reasonable explanation for the development of AN or BN, but the focus shouldn't be concentrated on these topics alone. It is probably better to regard eating disorders as heterogeneous which are influenced by an interaction of genetics and environmental conditions (Collier et al., 2004).

3.4. Risk factors

Bulimia nervosa and anorexia nervosa may be equally influenced by some risk factors, but there are also some factors which represent a specific risk for one or other of these disease-entities, such as dieting for anorexia nervosa (Collier et al., 2004). Fixed risk factors, such as genetics or environment, can be influenced by other factors, making it difficult to find the exact, individual effect of those fixed factors.

The most important socio-demographic risk factor for the development of anorexia nervosa has been identified as the female gender, with an odds ratio (OR) of 18.2. An interesting aspect to the development of anorexia nervosa lies in the socio-economic status of individuals. Families which are higher on the social ladder, such as white-collar workers, presented a higher OR than families receiving and living on social welfare. According to a study performed by Lindberg (Lindberg et al., 2003) identifying anorectic individuals living in Sweden, the ethnicity also played an important role. For instance, immigrant Asians and Africans had a lower OR (=0.4) for anorexia nervosa than children from native Swedish families. Lindberg et al (2003) furthermore described perinatal and prenatal occurrences as possible risk factors for the development of eating disorders, with perinatal risk factors showing an attributable risk of 3.6%, giving these factors only a marginal role in the aetiology of eating disorders (see table 3) Perinatal risk factors increasing the incidence of eating disorders are those such as premature birth, cephalhematoma, breech delivery, and premature rupture of membranes (Lindberg et al., 2003).

Category	Attributable risk
Gender	0.894
Socio-economic status	0.202
Etnicity	0.493
Psychosocial risk	0.076
Perinatal	0.036

Table 3. Attributable risk for eating disorders (Table modified from Lindberg et al., 2003).

The gestation age of children also has an influence on the development of anorexia nervosa. A birth occurring between the 23rd and 36th week of gestation results in a risk increase (OR=1.9). Pregnancies lasting at least 42 weeks have, according to a study conducted by Lindberg et al (2003), a lower risk of developing anorexia nervosa (Lindberg et al., 2003).

Another important risk for the development of anorexia nervosa or bulimia nervosa lies within the family. There seems to be a clear indication of a connection between parental psychiatric disorders and the development of eating disorders (Lilenfeld et al., 1998).

Further risk factors equally connected to and contributing to AN as well as BN are conditions characterized as anxiety, depression and obsessive-compulsive disorders, as patients suffering from these eating disorders have an elevated rate of lifetime risk of diagnosis of these clinical conditions (Kaye, 2007).

3.4.1. Genetics

With its beginnings in twin studies in the 1980s, the influence of genetics in the development of anorexia and bulimia nervosa has since been examined intensely. Current views on the aetiology of eating disorders regard the genetic influence as a major contributing factor (Collier et al., 2004). The vulnerability to suffer from eating disorders is modified by the genetic background, as these twin studies were able to show. The results indicated that the genetic influence on the development of eating disorder symptoms didn't have any effect on children younger than 11 years of age but in more than 50% of cases 17 year old twins, the genetic heritage was identified as a major contributing factor (Kaye et al., 2007).

Other related features to eating disorders, such as binge eating, self-induced vomiting, the drive for thinness, dieting and dietary restrictions also have a heritable background (Collier et al., 2004).

The fact is, that up to now no specific gen-loci related to eating disorders could be found. Nevertheless, some findings do support the theory of a genetically influenced aetiology. In anorexia nervosa drive for thinness and obsessionality are important traits (Collier et al., 2004) which were linked to chromosome 1 and chromosome 13 (Devlin et al, 2002). Chromosome 10 relates to bulimia nervosa and it also contains loci for obesity. This is a very interesting link, as an elevated family history of obesity can be found in bulimia nervosa patients (Collier et al., 2004).

Another interesting linkage between eating disorders and genetics is associated with the serotonin receptor gene HTR2A found on chromosome 13, which also carries information for the "drive for thinness" phenotype of anorexia nervosa (Delvin et al., 2002).

In addition, a further neurobiological influence can be found in the brain-derived neurotrophic factor (BDNF), which is suggested to be a susceptibility gene for anorexia nervosa (Collier et al., 2004).

3.4.2. OCD

Anorexia nervosa and bulimia nervosa are often combined with obsessive-compulsive behaviour which is too a characteristic risk factor for the development of these eating disorders (Kaye et al., 2007; Gonzalez et al., 2007). Usually, adolescents with AN are frequently described as perfectionists and high achievers, showing a high rate in extracurricular activities (Gonzalez et al., 2007).

OCDs are characterized as the result of childhood anxiety, which represents an "important genetically mediated pathway towards the development of anorexia nervosa and bulimia nervosa" (Zandian et al., 2007).

Supporting this statement are the following figures, showing the OCD occurrence in 94 patients struggling with anorexia nervosa. 35% of these young patients were diagnosed with OCD, of which 23% had OCD before the onset of AN. In conclusion, approximately 7% of patients eventually diagnosed with AN had OCD beforehand, showing that OCD is, in fact, rare before the onset of this eating disorder. In the USA childhood prevalence of OCD is reported to be about 2-3% (Kaye et al., 2004) and in the UK about 0.25% (Heyman et al., 2001). So far no evidence could be found that suggests a 10 times higher prevalence of AN in the US than in the UK, which would be the case if OCDs actually caused AN.

The incidence of OCD increases exponentially equally in boys and girls when they reach puberty, but adolescent girls are by far more prone to developing eating disorders than boys, once again suggesting only an inferior role of OCD in AN (Heyman et al., 2001).

It could be shown that AN patients have the highest rates of OCD and, compared to normal control woman and BN patients, increased rates of generalized anxiety disorders (Lilenfeld et al., 1998). BN on the other hand is significantly connected to increased rates of alcohol and drug dependencies (Gonzalez et al., 2007).

3.4.3. 5-Hydroxytryptamin (Serotonin)

Serotonin, also known as 5-Hydroxytryptamine (5-HT), is the best known inhibitor of food intake (Zandian et al., 2007) and is often associated with anorexia nervosa and bulimia nervosa. The question yet to be answered is, whether or not a deregulation of serotonin, a member of the monoamine system, could cause disturbances in eating behaviour. Agonists at the 5-HT^{2c} receptor are potent food intake inhibitors (Neary et al., 2004).

To measure the 5-HT brain metabolism, the cerebrospinal fluid was examined for 5-hydroxyidolacetic acid (5-HIAA), a metabolite of 5-HT and an indicator of brain serotonin turnover. Low levels of 5-HIAA were found in anorectic patients (Zandian et al., 2007), whereas in bulimic patients the CSF levels of 5-HIAA were normal compared to healthy control women (Kaye et al., 2007). However, this is thought to be the result of insufficient alimentation, resulting amongst other things in low tryptophan serum levels, an essential amino acid, and thus reducing the brain 5-HT turnover, rather than being the cause of eating disorders (Zandian et al., 2007).

Brain serotonin alterations are linked to characteristic changes in behaviour, especially psychiatric symptoms such as mood deregulations, impulse control deficit and appetite deregulation, symptoms also found in AN and BN patients (Kaye, 2007).

A relevant influence on serotonin especially important in young females in puberty, are estrogens, as they modulate serotonergic functions as well as stress-related neuropeptides such as cortisol releasing hormone (CRH) (Kaye, 2007).

3.5. Signs, symptoms and medical complications of anorexia and bulimia nervosa

The most obvious sign for AN is found in the disturbed eating behaviour of potentially affected individuals, as they are, in a nearly obsessive manner constantly preoccupied with food and eating. Weight preoccupation is a primary symptom in both AN and BN (Kaye, 2007; Mehler et al., 2004). In the fear of gaining weight AN patients will skip meals or reduce meal sizes, vomit or over-exercise (Gonzalez et al., 2007).

Usually, anorectic patients reduce their eating to a very low caloric intake per day and maintain this low level. In contrast, bulimic patients demonstrate nearly normal eating

behaviour however, after a period of dieting, these individuals lose control of their energy intake, resulting in overeating and subsequently in weight loss behaviour, such as the use of laxatives or diuretics or purging, as observed in the so-called purging-type BN (Kaye, 2007; Mehler et al., 2004). This binge/purge-cycle must occur at least twice a week, to meet the criteria of BN. This results in the characteristic fluctuation in body weight in this patient-group, who are usually not underweight (Gonzalez et al., 2007).

A medical complication results from frequent purging as bulimic patients may present epigastric pain and a sensitivity to hot and cold foods when enamel erosion is present (Gonzalez et al., 2007). These represent the most obvious oral complications of purging, usually found after six months of self-induced vomiting and reported in approximately 36% of bulimic patients (Mehler et al., 2004).

Furthermore, and especially in AN the endocrine system is affected by the substantial weight loss, most evident in females with onset of amenorrhea, which is characterized by an absence of the menstrual cycle for at least three consecutive months (Gonzalez, 2007). BN patients may present in cases of an active bulimia oligo-menorrhea, whereas amenorrhea is not found frequently (Mehler et al., 2004). In the case of menstrual irregularities in bulimic patients, lower 17ß-estradiol plasma levels were found compared to eumenorrheic bulimics (Monteleone et al., 2000).

Anorectic patients show a very high prevalence of osteoporosis, BN patients however only, if AN has occurred prior to the onset of BN (Mehler et al., 2004).

Further medical complications include electrolyte abnormalities, like hypokalemia. This state is not found very often in BN, just 4.6% of all cases, but nevertheless represents a very specific indication for BN in otherwise healthy women. Hypokalemia may lead to cardiac arrhythmias, muscle weakness or tetany. A special consideration in this matter must be taken in the case of co-existing hypovolemia, as potassium repletion can only be reached if the renin-angiotensin system is suppressed by a sufficient re-hydration of the patient. Otherwise, sodium is retained in exchange for hydrogen and potassium through the effects of the renin-angiotensin system. This is known as the pseudo-Bartter's syndrome (Mehler et al., 2004).

Acid-base abnormalities can also be observed in AN as well as in BN. Metabolic alkalosis can result from frequent purging, in which a constant loss of gastric acid and chloride ions contribute to the development (Mehler et al., 2004). Adipose tissue and lean tissue catabolism as a result of reduced energy intake and excessive exercising lead to ketoacidosis, as does the abusive use of laxatives (Casper, 2006; Mehler et al., 2004).

Sore throat, dyspepsia, dysphagia or hematemesis are symptoms found if the upper gastrointestinal tract, especially the oesophagus, is affected by the purging in bulimic patients. The misuse of laxatives in BN, often up to 50 pills a day, can result in an atonic colon, chronic constipation and hence lead to laxative dependency (Mehler et al., 2004).

3.6. Therapy of AN and BN

Generally, the treatment of AN is very difficult, as 30% of all affected patients do not recover from the disorder and the time needed from diagnosis to recovery is about 6 years (Morris et al., 2008). Furthermore, no strong evidence based treatment guidelines are available (Zandian et al., 2007). Especially treatment inside a facility like the hospital is associated with poor therapy outcome and reduced long term success (Morris et al., 2008). The therapy of AN and BN should be managed by a multidisciplinary approach, as these disorders involve physical and psychiatric entities (Mehler et al., 2004).

Support for the affected individuals is very important. This relationship was demonstrated impressively by a study which showed a 100% dropout rate in anorectic patients, when they were not supported during dietary adjustments (Morris et al., 2007). Including the family in the therapy is too a very important issue. Therefore it is suggested to involve all family members in the treatment, as it influences the 5-year outcome positively. In family-based treatment regimen, 6 out of 10 patients will profit compared to only 1 out of 10 patients, whose family is not involved in the therapy (Zandian et al., 2007).

Another approach is a cognitive behavioural therapy, however results have been disappointing so far. Only 14% of bulimic patients would benefit from a cognitive behavioural therapy and stay in remission 4 months after treatment (Zandian et al., 2007).

Diverse opinions on the role of psychotherapy in anorexia nervosa are discussed. The New Zealand study of cognitive behaviour therapy and psychotherapy showed no significant benefit for the patients (Morris et al., 2007). However, Gee et al (1999) demonstrated a

positive connection between the treatment of OCD, a psychiatric condition very often connected to AN, with Prozac and the increase of body weight and a general improvement in symptoms (Gee et al., 1999).

4. Obesity in childhood and adolescence

According to data collected between the years of 1999 and 2000, the prevalence of childhood and adolescent obesity has risen by 38% from 1988 to 2000, with a value of 12.7% in 12 to 19 year-olds (De Ferranti et al., 2007). Other figures indicate that in the United Kingdom 7-8% of adolescents are seriously obese with 15% being seriously overweight but not obese (Dasha et al., 2005). In the United States and the United Kingdome 60% to 70% of adults are overweight and half of these adults again are classed as obese (Li et al., 2008).

Obesity is a rising health issue among the younger generation and is often considered part of the metabolic syndrome, responsible for an increased risk of type 2 diabetes and cardiovascular disease (Ferranti et al., 2007).

The expression obesity refers to an excess of body fat or, less accepted as a diagnostic definition, an excess percentage of fat contributing to total body weight. Usually to define obesity in childhood, adolescence and in adults the BMI and bodyweight are used, whereas the BMI is the preferred method of evaluation of obesity in patients between 2 and 19 years of age (Krebs et al., 2007).

4.1. The BMI

It is only since 1997 that the WHO has accepted the fact that obesity is a major and ever growing health issue in modern society and that it may lead eventually to serious health problems. Back then, the BMI was selected as the appropriate system of measurement to identify affected people (James, 2008).

The body mass index is easily calculated or determined from published tables or nomograms (Thomas et al., 1976) and is therefore a popular method for the evaluation of obesity, especially in adults. It expresses the weight-for-height relationship as a ratio - the unit being kg/m^2 - and offers a number of advantages, as weight and height are regularly measured and are therefore readily available. As a result of the simplicity of this measuring system, high reliability in the achieved results can be expected (Dietz et al., 1998). An important factor to be considered in the assessment of this ratio is that the BMI can't be interpreted equally for all age groups. Therefore, in children and adolescents percentiles

are available for the measurement and calculations of the BMI. Values over the 95th percentile are regarded as obese, comparable to BMI-values exceeding 30kg/m², whereas overweight in children and adolescents is defined by a BMI larger than the 85th percentile and lower than the 95th percentile (Krebs et al., 2007). The BMI is an important value because of its link to risk factors and morbidity associated with overweight (Dietz et al., 1998).

Despite the easy calculation of the BMI, values do not necessarily correlate 1:1 with body fat, as several studies pointed out, showing that the BMI is a somewhat imprecise measure when it comes to the estimation of body fat (Dietz et al., 1998). Kuczmarski and colleagues (2000) present BMI percentiles for boys and girls (Kuczmarski et al., 2000).

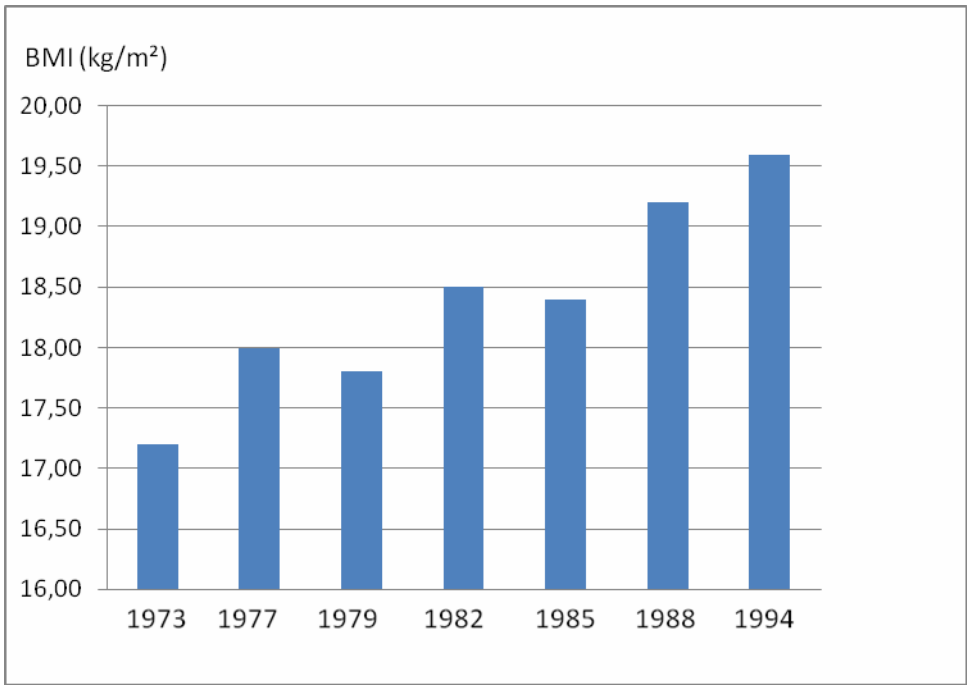

Diagram 1. BMI development in 10 year old boys from 1973 to 1994 (modified from Nicklas et al., 2001).

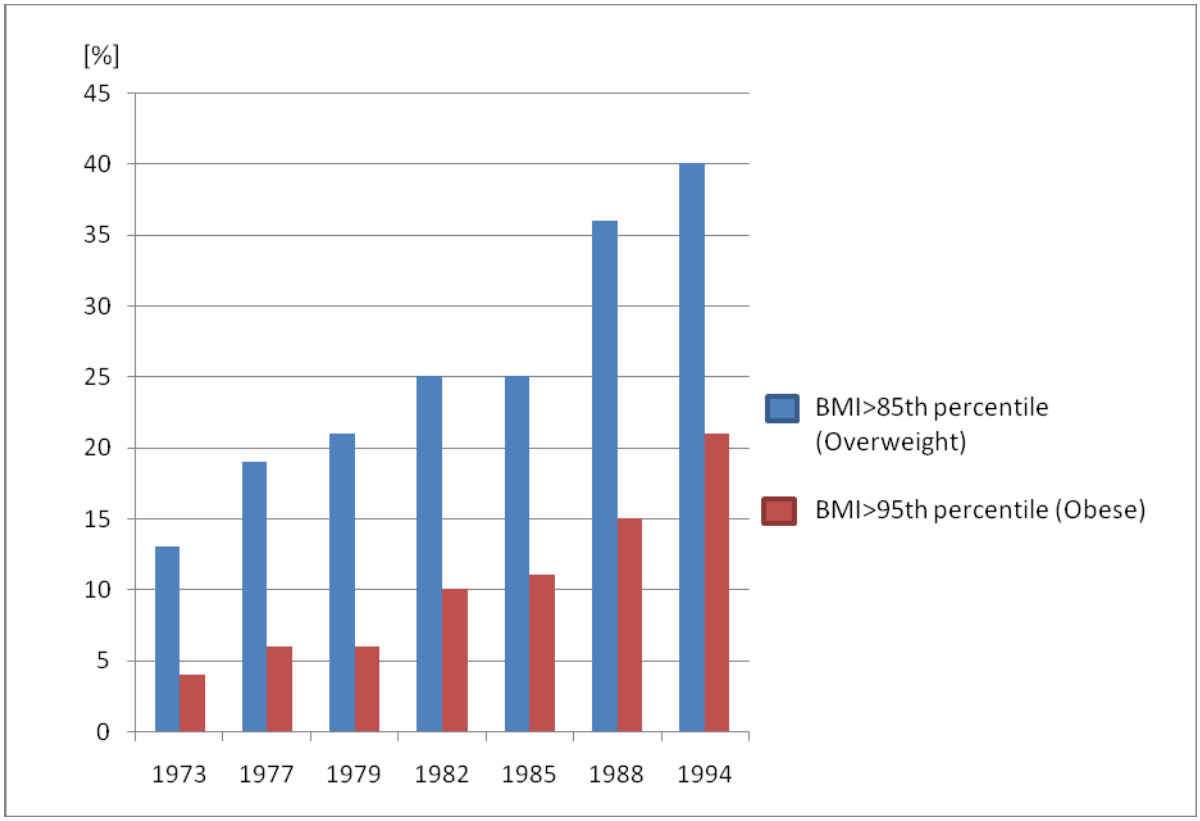

Diagram 2. Percentage of overweight and obese 10 year olds from 1973 to 1994 (modified from Nicklas et al., 2001).

4.2. The metabolic syndrome

In general the metabolic syndrome can be summarized as an imbalance of many different metabolic values. Many organisations, such as the WHO, the International Diabetes Federation, the National Cholesterol Education Panel and other, have created identification criteria for this metabolic disorder with only minor differences. Taking a closer look at the World Health Organisation (WHO) definitions, the main and obligatory point for the definition of the metabolic syndrome are all grades of glucose metabolism disorders, beginning with impaired glucose tolerance up to the full phenotype of type 2 diabetes, with excess fasting plasma glucose levels. Other criteria, common to all of the organisations' definitions, include an elevated systolic blood pressure of 130 – 140 mmHg, fasting triglycerides over 150mg/dl, and an HDL-Cholesterol lower than 35-40 mg/dl in men or lower than 50 mg/dl in women. The BMI, another definition factor for MS by the WHO, exceeding a value of 30kg/m² also indicates the possibility of a metabolic imbalance. Another factor giving a reason to think of metabolic syndrome is the amount of albumin excreted in the urine. An excretion rate of more than 20µg/min or an albumin-creatinine

ratio over 30mg/g should be taken as serious indicators. Further definitions for the metabolic syndrome for adults include a waist circumference larger than 94-102cm in Europoid men or values exceeding 80-88cm in Europoid women (de Ferranti et al., 2007).

4.3. Epidemiology

Childhood obesity is a major contributing factor in the development and increase of the metabolic syndrome in children and adolescents. The metabolic syndrome, a certain combination of medical disorders and the consequence of obesity, increases the risk for cardiovascular diseases and diabetes mellitus. It is to believe that a rise in prevalence of metabolic syndrome in childhood leads to an increase of obesity associated complications in adolescence, such as diabetes mellitus type 2. Since the 1960's the obesity rates in the United States have tripled and a BMI over the 85th percentile is reached in up to 50% of 6-19 year olds (de Ferranti et al., 2007).

According to Hedley et al (2007) the prevalence of overweight children between 6 and 19 years of age, living in the United States, lies at 16% (Hedley et al., 2007).

The calculation of the prevalence showed, depending on the definition criteria used, high instances of variability. For example, the WHO definition does not include the measurement of the waist circumference, which could potentially lead to overlooking children and adolescents possibly affected and thus resulting in different prevalence values. A commonly observed fact resulting from an increase in rates of obesity - not only in adults but also in children and adolescents - is supported by an analysis of the year 2000 in which 12.7% of 12 to 19-year-olds were identified as having the metabolic syndrome. This was an increase of 38% compared to the prevalence which had been calculated 6 years earlier. An even higher prevalence of the metabolic syndrome is found in overweight and obese children of all ages, as the following numbers indicate. 32.1% of adolescents with a BMI over the 95th percentile, 7.1% among those children with a BMI between the 85th and 95th percentile were shown to fulfil the criteria for the metabolic syndrome, whereas only 0.1% of the affected had a BMI lower than the 85th percentile (de Ferranti et al., 2007).

The socioeconomic status does play a role in the development of obesity, although women are more often affected by this inverse relationship than men. But this factor doesn't have a big influence on children and adolescents. Although this relationship is generally very weak, the lowest prevalence of overweight is found in families which have a history of

more than 13 years of education history, but this accounts only for non-Hispanic whites (Troiano et al., 1998).

4.4. Aetiology of obesity

4.4.1. Food and energy intake

It is difficult to assess correct values from questionnaires and self reporting due to the fact that, according to a survey conducted between 1994 and 1998 in the US, 55% of the children between 3 and 19 years of age reported implausible values. However, of those who actually did report plausible caloric intake it had a positive correlation to their BMI (James, 2008).

According to an analysis conducted over 20 years, the BMI and the prevalence of overweight and obesity has gone up consistently, but interestingly enough, no increase in total energy intake has been noticed. What has changed however is the food composition. The percentage of fat in total caloric intake has decreased over time, from 38% to 33%, and the percentage of carbohydrates and protein has increased. But still, maximum recommended fat consumption was exceeded by an impressive 75% of children in 1994. This is mostly to an increase of fat consumed from poultry, cheese, and snacks. As the dietary causes of obesity are very complex and not very well understood, a precise identification of aetiological eating patterns has yet to be found (Nicklas et al., 2001).

But it seems obvious that energy homeostasis is the key role in maintaining a healthy bodyweight (in regards to the BMI: 20.1-24 kg/m²), as physical activity increases energy expenditure and may contribute to a negative energy balance, important for weight-loss.

4.4.2. Predisposition

One interesting predisposition in the development of childhood adiposity lies in the mother's pregnancy with that child (Dabelea, 2007; James, 2008). High serum glucose levels in the pregnant woman lead to an increase in the fetal glucose serum levels, because glucose can freely pass the placenta. Insulin however does not pass the placenta, which forces the fetal pancreas to produce more insulin, which not only reduces the serum glucose level, but also acts as a fetal growth hormone, possibly leading to adiposity. Following the development of new-borns up to the age of eight of mothers diagnosed with

diabetes, showed that these children were on average 30% heavier than expected for their age (Dabelea, 2007).

Another factor during pregnancy which possibly contributes to an increase in the chance of higher BMI values in children and adolescents was found in a vitamin B12 deficiency. The lower the B12 levels, the smaller and fatter the newborns are and the risk of insulin resistance rises. This could, together with other prevailing environmental conditions, subsequently lead to these individuals developing the metabolic syndrome when they grow up. On the other hand, in the broadest sense of predisposition, there are also protecting-factors, such as breast feeding, which reduce the risk of overweight in children. The energy uptake while breast-feeding is highly dependent on the baby itself, because it eats at its pleasure and not more. However, many mothers do not take advantage of this self regulation and over feed children, the reason being, according to James (2008), in the mother's lack of understanding of how much energy the breast-fed milk actually has (James, 2008).

4.4.3. Physical Inactivity

The main problem in modern society seems to be the reduction in the need for energy expenditure, for instance the more frequent use of cars or doing jobs at home in front of the computer, leaving no doubt that the incentive to be active in daily living has declined. One estimates that the caloric expenditure has dropped by approximately 250-500 kcal per day over the past 50 years (Fox et al., 2007).

Fox et al (2007) do also point out that the danger of physical inactivity lies in its implications in the increased risk of overall mortality. This includes diseases such as coronary heart disease, stroke, diabetes and even cancers. Physical activity - most effective are activities of moderate and vigorous intensity - (Department of Health, Physical Activity, Health Improvement and Prevention) reduces the risk of cancer, however the mechanisms of the inhibition of carcinogenesis are yet to be understood (Rogers et al., 2008).

Physical activity is an important factor for staying healthy and fit. This also counts in serious cases of overweight and obesity, as physical activity reduces the risk of the above mentioned diseases and thus reduces morbidity and mortality in overweight patients and

consequently – another very important issue – health care costs. These have been numbered at 8.2 billion pounds Sterling per year (Fox et al., 2007).

4.4.4. Genetics

It seems obvious that the genetic heritage plays a significant role in the development of overweight in the children of parents themselves struggling with overweight. Evidence for this can be found dramatically in adopted twins (Farooqui et al., 2006). Studies on twins suggest a genetic involvement of over 50% in variations of BMI (Knecht et al., 2007). Although many gene-loci have so far been identified as possible aetiological factors in the pathogenesis of obesity, only a few genes have convincingly been confirmed as a reason for obesity. One estimates, that the BMI of children is influenced by the genetic background by about 40%-70% (Li et al., 2008).

An impressive example showing the involvement of genes in obesity are the so called Pima Indians living in the south-western desert of Arizona, an area restricted in nutrients. This special population had no weight problems a century ago, but now over 75% of Pima Indians are obese and the prevalence of DM-II is higher than 45%. The reasons for this are that the genetic basis hasn't changed, resulting in low level of insulin-secretion and an increased insulin sensitivity, and the now abundant food supply, leading to increased calorific intake (Knecht et al., 2007).

An interesting theory of the composition of our genome is, that during evolution our genome adapted to situations in which food was rare and could only be obtained with a lot of physical effort. At present, food is available in abundant supply, and considering the mentioned theory of our genome, the current social situation therefore may predispose the development of overweight and obesity (Li et al., 2008).

One estimates that 127 genes are in some way responsible for or at least influence the development of obesity. Although 10 studies have agreed that 12 of the 127 obesity related genes are associated with overweight the general implication of these genes is still controversially discussed. 400 genes have been identified as being associated with weight-control mechanisms (Knecht et al., 2007).

Nevertheless, a few genes should be mentioned, as many association-studies were able to point out the connection between genetic variations of genes with overweight. One

significant genetic variation is found in the DNA segment encoding the melanocortin 4 receptor (MC4R) (Farooqui et al., 2006). The MC4R normally acts as an anorexigenic receptor and plays a key role in energy homeostasis by inhibiting food intake. This gene is however the most frequently affected gene in association with obesity, responsible for approximately 5% of severely obese children (Li et al., 2008).

Another possible genetic cause in the development of obesity and insulin resistance was described in variations of the ectoenzyme nucleotide pyrophosphate phosphodiesterase (ENPP1) -gene The miss-sense variant K121Q, by potentiating the normal function of the ENPP1-encoded protein, which normally inhibits the insulin-induced activation of the insulin receptor, increases the risk for the development of diabetes mellitus type 2 as early as in childhood (Meyre D. et al., 2005; Farooqui et al., 2006).

Uncertain involvement of interleukin-6 (IL-6) in the pathogenesis of obesity is currently also under discussion. A possible aetiological involvement in obesity may be found in a chronic low-grade activation of the immune system, in which the cytokine IL-6 plays an important role (Li et al., 2008).

4.4.5. Drug related body weight

Unpleasant side effects from commonly used drugs are the influence on homeostatic mechanisms controlling body weight and hence leading to overweight. Such drugs are - among others - atypical neuroleptics, antagonizing anti obesity agents at catecholamine receptors. Also antidepressants, such as the older tricyclic-agents amitriptyline and mirtazapine, have the effect of weight gain. Furthermore, some serotonine reuptake inhibitors (SSRI) promote an increase of weight. Knecht et al (2007) further summarize that carbamazepine, valproate and gabapentine – all used in anti-epileptic therapy – promote weight gain. Lithium, a drug mainly used for psychiatric reasons, also leads to weight gain. Some SSRIs however are said to reduce weight so do topiramate (anti-epileptic drug and in the therapy of migraine) and zonisomide (anti-convulsive therapy) (Knecht et al., 2007).

4.4.6. Neurobiological influences on caloric intake

In summary, following factors influence calorific intake and consequently body weight gain:

Neuropeptide Y (NPY) - NPY is a fast acting small orexigenic peptide responsible for food intake initiation. It is co-secreted – along with other hormones - with catecholamines.

Ghrelin - A hormone produced in the stomach that interacts with the hypothalamus leading to a secretion of NPY and AgRP, resulting in a rise of appetite and food intake initiation.

Insulin – Depending on the mode of administration, insulin leads to adverse effects. Insulin induced hypoglycaemia for instance, increases food intake, and centrally infused insulin decreases energy intake (Knecht et al., 2007).

For further details, see chapter 2 "Neuropeptides controlling appetite".

4.5. Treatment and prevention of obesity

Looking at physical activity in relation to overweight and obesity two views must be looked at separately. The first view - and less susceptible to physical activity - is the prevention of obesity and the second view is the treatment of obesity with the promotion of activty. According to Fox and his colleagues (2007) only little is known about the effectiveness of an increased energy expenditure on the prevention of obesity, so that one can't for sure identify activity as a protecting factor. However, physical activity, combined with an adequate adaptation of dietary behaviour, is an effective measure in the treatment of already existing overweight (Fox et al., 2007).

Therefore it's a very important issue in the treatment of obesity to promote physical activity, and thus increase daily energy expenditure. Especially promoting leisure time physical activity and encouraging the involvement in sport groups should be thought of, as physical activity at home and at work have reduced in today's society (Fox et al., 2007). Significant positive effects of physical activity on body weight are generally reported (Davis et al., 2007).

Drug treatment may also be an option in the treatment of obesity. Orlistat – a reversible lipase inhibitor which reduces cholesterol and triglyceride uptake- and sibutramine – a reuptake inhibitor of serotonin, norepinephrine and dopamine acting as an appetite suppressant- are drugs approved for the use in paediatric patients (Nicholls et al., 2005; Spear et al., 2007). But a medication therapy should always be part of a general lifestyle

modification, because only then weight loss of approximately 5% to 10% can be achieved (Spear et al., 2007). The most bothering side effects of orlistat are oily bowel movements and flatus.

4.6. Consequences of obesity

In 1981 it was estimated that 35% of all cancers in the United States were due to poor diet and a consequence of physical inactivity (Rogers et al., 2008).

In summary, obesity may result in following consequences (modified from Knecht et al., 2008):

- Neuropsychiatric: Depression, poor self esteem and social isolation
- Neurological consequences such as stroke, dementia or obstructive sleep apnoea
- Pulmonary consequences like asthma or exercise intolerance
- Cerebro-cardiovascular consequences like chronic inflammation, microangiopathy, makroangiopathy, and hypertension
- Endocrine consequences include disorders such as insulin resistance or glucose intolerance, type II diabtes
- Muscularskeletal consequences such as joint pain, tibia vara or flat feet

5. ADHD

5.1. Introduction

Attention Deficit Hyperactivity Disorder (ADHD) is a very frequently diagnosed psychiatric disorder in children in all parts of the world, it includes symptoms such as inattention, impulsivity, and hyperactivity (Biederman et al., 2005; Smoot et al., 1998) hereby affecting the quality of life of the affected children (Escobar et al., 2008). Due to the connection with partially severe co-morbidities, the identification of this disorder is of essential importance.

5.2. Epidemiology

Approximately 4-8% of children worldwide are affected by ADHD, whereby a higher incidence in the male gender is reported. According to Polanczyk and colleagues (2007), male prevalence of ADHD is 2.45 times higher than in girls. Females are predominantly affected by the inattentive form (Smoot et al., 2007). This disorder always begins in childhood (Greenhill, 1998) and could possibly persist up to adulthood (Biederman, 1998). Generally, one cannot make a clear conclusion about the prevalence as many studies have calculated figures ranging from 0.9% to up to 20%. Polanczyk et al (2007) have however concluded from an analysis based on 102 studies from around the world, that the prevalence of ADHD in children and adolescents is 6.48% and 2.74% respectively (Polancyk et al., 2007).

A very important issue in the interpretation of ADHD prevalence-values is to be found in the diagnostic criteria, as these can significantly modify the results. Furthermore, including or excluding impairment caused by ADHD from the diagnostic criteria (as this difference is found between the DSM-IV and the ICD-10) also influences the prevalence. For example, several investigations defined ADHD without the presence of any impairment, while others used – partly different – definitions of impairment, leading to a prevalence varying between 3.7 to 8.9% (Polanczyk et al., 2007).

ADHD may persist, upon onset in childhood, right up to adulthood, however exact numbers are not mentioned, but, despite this, one estimates the number of persisting ADHD in adults to lie between 15% and 60%, depending once again on how many symptoms are used for the diagnosis. ADHD in childhood especially implies a higher risk

of a series of psychiatric disorders, such as major depression or tics or the Tourette syndrome (Polancyk et al., 2007).

The impact of socio-economic, ethnic and cultural influences on the development of ADHD hasn't been the subject of many studies so far. However, observations up to the present seem to favour an independency of the prevalence of ADHD from the above mentioned possible influences (Polanczyk et al., 2007).

5.3. Diagnosis of ADHD

5.3.1. The DSM-IV and ICD-10 diagnosis criteria and core symptoms

Two partly diverging diagnostic criteria schemes, the DSM-IV (Diagnostic and Statistical Manual of the American Psychiatric Association,4th edition) and the ICD-10 (International Classification of Diseases, 10th edition) are used for the diagnosis of ADHD, whereby the DSM-IV classification allows the identification of three subtypes of ADHD: mainly inattentive, mainly hyperactive-impulsive, or both combined (Biederman et al., 2005).

The DSM-IV and the ICD-10 use the same diagnostic criteria consisting of 18 points, but while the DSM-IV speaks of Attention Deficit Hyperactivity Disorder (ADHD) the ICD-10 rather uses the term Hyperkinetic disorder (HKD). These 18 common points for identifying ADHD or HKD consist of 9 symptoms characterising inattention, 6 symptoms identifying hyperactive traits and 3 symptoms of impulsivity, all implicating the possibility of an impairment to school performance, intellectual functioning or social skills (Schacher et al., 2007; Biederman et al., 2005; Laurence, 1998). Despite using the same 18 criteria points the altered interpretation of these symptoms by the DSM-IV or ICD-10 lead to quantitatively and qualitatively different results (Schacher et al., 2007). The number and type of symptoms necessary for the diagnosis of either HKD or ADHD differ, depending on which classification system is used.

Criticism arose in the past concerning the fact that children were falsely diagnosed with ADHD, because of the low threshold of the DSM-III-R criteria and thus led unnecessarily to treating allegedly affected children. Therefore, in the DSM-IV classification, following points were introduced in order to increase the specificity of the diagnosis of ADHD at the cost of some sensitivity (Greenhill, 1998):

1. It is necessary to differentiate between a predominantly inattentive subtype, a hyperactive subtype and a combined type
2. The symptoms must be present in a structured environment, like school or at work
3. The symptoms must cause a significant impairment in social or academic functioning

The following table shows the 18 common symptoms, 9 characterising inattention symptoms and 9 others hyperactivity-impulsivity symptoms, which are used by the ICD-10 and the DSM-IV to identify HKD and ADHD, respectively.

Inattention symptoms:	*Hyperactivity-impulsivity symptoms:*
▪ Inattentive to details/makes careless mistakes	▪ Fidgets or squirms
▪ Difficult sustaining attention	▪ Leaves seat when should remain seated
▪ Seems not to listen	▪ Runs or climbs excessively
▪ Does not follow through and complete tasks	▪ Difficulty playing quietly
▪ Disorganized	▪ 'On the go' or acts as if 'driven by motor'
▪ Avoids/dislikes tasks requiring sustained attention	*Impulsivity symptoms:*
▪ Often loses necessary things	
▪ Distractible	▪ Talks excessively
▪ Forgetful	▪ Blurts out answers
	▪ Difficulty waiting in lines/awaiting turn
	▪ Interrupts or intrudes on others

Table 4. DSM-IV and ICD-10 definition criteria (modified from Lahey et al., 2006).

Criteria that have to be met for the ICD-10 are at least 6 inattention symptoms and at least 3 symptoms of hyperactivity. Furthermore, at least 1 impulsivity symptom must be observed in the affected child. These criteria symptoms must be mentioned independently by parents and teachers by the latest at the age of 7 and must result in a functional impairment in home and school settings. The DSM-IV has a similar approach to the identification of ADHD. Here 6 or more inattention symptoms and more than 6 hyperactivity-impulsivity symptoms must be present and be reported. In contrast to the ICD-10 interpretation where the symptoms must be reported independently, the DSM-IV

adds up all mentioned symptoms by parents and teachers (Lahey et al., 2006). Furthermore, the ICD-10 defines mood, anxiety and developmental disorders as exclusion criteria from the diagnosis of ADHD (Polanczyk et al, 2007).

Further important differentiating factors can be found between the two classifications. According to Lee and colleagues (2008) the most obvious consequence of the different approach to diagnosis lies in the prevalence of HKD and ADHD, whereby ADHD – defined by the DSM-IV - is 20 times more prevalent than HDK (Lee et al., 2008).

Despite some differences in the classification systems, the identification of ADHD by using either of which, when made by a well trained professional (Biederman et al., 2005; Conners, 1998), is reliable and shows a predictive validity for HKD and ADHD (Lahey et al., 2005).

5.3.2. Questionnaires and rating scales

Once the possibility that a child could be affected by symptoms characterised as part of ADHD has been confirmed, further assessment is necessary. For this purpose, several methods are available to clinicians such as questionnaires and rating scales (Smoot et al., 2007).

An important issue in the diagnosis of either ADHD or HKD lies in obtaining information from several sources. This allows for more precise identification. Usually it is parents and teachers who provide the most and - more importantly – most reliable results, although the results are not always congruent. Children on the other hand do not represent a reliable source (Polanczyk et al, 2007).

Obviously the diagnosis and treatment shouldn't be entirely based upon the interpretation of questionnaires and rating scales but nevertheless, a short summary of several advantages ought to be mentioned (Conners, 1998):

1. Observing a child over a long period of time allows clinicians to collect data in diverse situations and circumstances and hence collect data on common and rare behavioural patterns.
2. Many scales already exist and are cost and time efficient.
3. They allow an easy assessment of quantitative and qualitative behavioural aspects from direct relatives as well as from "significant others" (e.g. teachers).

4. Rating scales have proven to be drug-sensitive and can therefore show the effectiveness of a treatment.

Conners (1998) also mentiones a number of disadvantages, which are as follows:

1. Leniency errors: The true severity or frequency of an observed behaviour is judged too leniently.
2. Severity errors: The exact opposite of disadvantage pointed out under 1.
3. Halo errors: Basing the rating of all items on account of a single behaviour.
4. Logical errors: The observer will rate a certain item as a result of a different item he or she had rated previously, just because they feel it must logically follow.
5. Contrast errors: Comparing a certain child's behaviour to others may change the rating, depending upon whom the child is compared to. This error especially affects the prevalence of ADHD.
6. Recency errors: This error describes the tendency to rate a child according to the most recent episode of behaviour.

5.4. Aetiology

5.4.1. Risk factors

One can summarize the risk factors for ADHD in prenatal, perinatal and postnatal risk factors or environmental and genetic factors. A seemingly major contributing factor to the development of ADHD is made during the pregnancy with the child. Maternal smoking has been identified to increase the risk for ADHD by up to a 3 fold compared to non smoking pregnant women, resulting in an odds ratio of 1.3 (Banerjee et al., 2007).

Also an environmental and avoidable risk factor during pregnancy is alcohol consumption by the pregnant woman. Alcohol exposure during pregnancy may cause cerebral anomalies, often described as a cause for ADHD. Problems in children and adolescents which are associated with in utero alcohol exposure are learning problems, inattention, and a generally impaired intellectual performance (Banerjee et al., 2007).

5.4.2. Neurobiology and Genetics

Several attempts have been undertaken to find neuro-anatomical or neurobiological anomalies in ADHD affected individuals. Often found in MRT analyses are reduced corpus callosum, abnormal caudate asymmetry or reduced total cerebral volume. In

adolescent and adult ADHD patients, PET research found significant decreases in brain metabolism, especially affecting the basal ganglia which are an important finding, given the possible implication of the corticostriatal circuits in the pathology of ADHD.

The risk to suffer from ADHD if a parent had the very same disorder is 6.6 times greater for girls and 1.5 times higher for boys, suggesting that girls are a lot more vulnerable in this matter. Adoption studies or twin studies were also very conclusive in respect of a genetic background of this disorder, as a concordance rate of 51% in monozygotic twins could be reported (Zametkin et al., 1998).

5.5. Co-morbidities in ADHD

5.5.1. Sleeping problems

Besides the thoroughly discussed symptoms in the diagnostic criteria of the ICD-10 and the DSM-IV, ADHD is often found to be connected to several other conditions, impairing the quality of the child's life. It is commonly reported that children affected with ADHD or HKD have impaired social or academic functioning, reasons for this also to be found in other psychiatric conditions (Pliszka, 1998; Sung et al., 2008; Spencer, 2006).

One possible factor influencing the behaviour of a child affected with ADHD is postulated in the sleeping pattern of these children, as children with ADHD have, compared to children without this diagnosis, greater difficulties in behavioural, social and academic functioning. Sleeping problems affect approximately 3 out of 4 children with ADHD, whereas problems predominantly lie in the difficulty falling asleep, resistance to going to bed and tiredness on waking. A study conducted by Sung and colleagues (2008) revealed a connection between sleeping problems and reduced psychosocial scores and a lower quality of life in ADHD affected children and furthermore associated the severity of ADHD symptoms with sleeping problems (Sung et al., 2008).

5.5.2. Psychiatric disorders connected with ADHD

Many studies have shown the connection of ADHD with other disorders, especially of psychiatric nature. These include disruptive behaviour disorders, depressive disorders

(classified as unipolar disorder), bipolar disorders, anxiety disorders, and learning disorders (Spencer 2006; Pliszka, 1998).

5.5.2.1. Mood disorders

Mood disorders can range from depression to mania, sometimes the predominant symptoms shift from the one to another. Children diagnosed with depression may in time convert to individuals affected with mania. This was concluded from several studies, which identified 20% to 50% of children where the depression diagnosed in the first place converted to mania. This high conversion rate is unusual. Physiological disorders such as changes in appetite and weight, loss of interest in favoured activities, school difficulties or refusal, and antisocial behaviour are connected to depression. 29% of children have a depression when first diagnosed with ADHD, which usually is before the age of 7. Interestingly, the lifetime rates for depression rises after time up to 45% by the age of 15 years (Spencer, 2006).

An influencing factor to the development of depression in ADHD children is found in the family background. Mood disorder symptoms found in the parents raises the risk for depression in ADHD children. Pliszka (1998) reports on the findings from surveys indicating that parents may often be unaware of the depression of their child (Pliszka, 1998).

Many symptoms such as mania and ADHD overlap, making it difficult to differentiate between the two, but manic children seem to present the symptoms in a more regular, chronic form rather than the acute or episodic character of ADHD children (Spencer, 2006).

5.5.2.2. Anxiety disorders

Typically, 25% to 33% (Jensen et al., 2001) of children affected with ADHD also present anxiety symptoms and are older at the time of presentation than children with ADHD alone. As with depression, parents are often unaware of the condition of their child, and it is thought, that the children might be more important in making the detection of a co-morbid association. Generally, it is reported that children combining ADHD with anxiety disorders have a higher impairment in their quality of life, reaching from more school

problems (however no differences in school performances) to a wider range of social problems (Pliszka, 1998).

A careful assessment of symptoms must be undertaken, due to the high risk of misinterpretation. Many anxiety symptoms, like agitation, tantrums, or attention-seeking, overlap with symptoms seen in ADHD patients (Spencer, 2006).

5.5.2.3. Learning disabilities

Between 40% and 60% of children diagnosed with ADHD are identified as having learning problems, whereby 20% to 30% are disabled in the areas of reading, spelling, or arithmetics (Pliszka, 1998). This connection has been often demonstrated, as these children repeat a year more often, achieve poorer marks in academic subjects or have more additional tutoring The reason for the learning disabilities, such as reading problems, may be inherited independently from ADHD, as twin studies have shown (Spencer, 2006).

5.5.2.4. Defiant behaviour and conduct disorders

Several studies state a co-occurrence for defiant behaviour or conduct disorders in up to 50% of children with ADHD. This represents a major problem, as especially conduct disorders very often lead to social failure or delinquency (Spencer, 2006).

Children with conduct disorders and ADHD appear to be more aggressive and to slip more often into delinquency in their adolescence. One reason may lie in the significant differences in academic achievements of these co-affected children. 36% of children presenting a combination of reading disorders and ADHD are also diagnosed with conduct disorders. This percentage is about 5 times higher than the percentage found in a control group (Pliszka, 1998).

5.5.2.5. Substance use

A very common combination with ADHD is substance use, especially in adolescence. ADHD affected children are at a very high risk of cigarette, alcohol and psychoactive substance use as early as before their 16th birthday (Spencer, 2001; Bukstein, 2008). The lifetime risk of eventually falling into dependency of one of the mentioned addictions is stated to be as high as 50%.

An interesting observation is mentioned by Bukstein (2008) that 15% to 25% of adults treated for substance use were diagnosed with ADHD in their childhood. An effective prevention from substance use is the controlled pharmacotherapy of ADHD. As an affected ADHD child grows up, maintaining the ADHD therapy becomes more and more complicated, thus - if not well managed - increasing the risk of substance use in adolescence and later in life (Bukstein, 2008).

5.5.2.6. Tic disorders

Tic disorders are more often seen in children with ADHD, but they do not seem to contribute additionally to the impairment character of ADHD itself and furthermore only have a little impact on the course of ADHD compared to the severity of some other co-morbidities. And finally, tic disorders usually disappear after time (Spencer, 2006).

5.6. Therapy

The main goal of therapy of ADHD affected children focuses on the improvement of social interactions and overall behaviour. To this end, two main approaches are considered as appropriate. First line treatment involves medication, such as stimulants like methylphenidate, the second option includes behavioural interventions in addition to medication (Smoot et al., 2007).

5.6.1. Medication

5.6.1.1. Stimulants

Pharmacological stimulant therapy is an often chosen treatment regimen in children with ADHD, especially in the absence of co-morbidities (Smoot et al., 2007), this being due to the frequently documented safety and tolerability of this therapy option (Findling et al., 1998). However, Wigal et al (2006) document in their study that 11% of ADHD patients treated with methylphenidate (MPH) had shown adverse events, a percentage, far beyond the expected 1% reported prior to the examination. Adverse events such as appetite and sleep problems, two often documented events, as well as less frequent signs such as social withdrawal (Wigal et al., 2006) appear dose dependently (Findling et al., 1998).

Stimulants increase the sympathomimetic and CNS activity by increasing the dopamine and norepinephrine concentration in the presynaptic neurons. Among several available stimulants, methylphenidate is suggested as the first line therapy, because of its safety record (Smoot et al., 2007).

5.6.1.2. Non-stimulant therapy

Non-stimulant therapy with atomoxetine should only be considered after unsuccessful trials with stimulants, as the effect on ADHD is smaller than methylphenidate. Atomoxetine appears to be a relatively tolerable treatment option, as in a 2-year observation of more than 600 treated patients only 5.2% had discontinued the use of the medication (Smoot et al., 2007).

5.6.2. Behavioural intervention

Behavioural therapy in combination with medication improves ADHD symptoms and even affects family members positively. To achieve a reduction in the dosage of medication and an improvement of the core symptoms of ADHD, behavioural therapy should be opted for as an additional treatment regimen alongside medication (Smoot et al., 2007).

6. Leptin in eating disorders, obesity and ADHD

6.1. Anorexia nervosa & Bulimia nervosa

6.1.1. Physical activity in anorectic and bulimic patients

Increased levels of physical activity in patients with AN have been reported in many studies and reviews and is considered as a major clinical indication for the existence of AN and as a potential risk factor in the development of AN (Holtkamp et al., 2005; Zandian et al., 2007). Furthermore, there seems to be a direct connection between activity and the grade of starvation of an individual patient (Hebebranda et al., 2003). One would normally expect emaciated and starving individuals to be lethargic and slow, but the striking opposite is the case in anorexia nervosa (Casper, 2006). Nevertheless, van Elburg et al (2007) do emphasize, that the state of agitation and restlessness does in fact die off in the final stages of starvation and patients become lethargic (van Elburg et al., 2007). This so called '2 step process' displays an initial phase with reduced energy intake, high physical activity, and increased productivity, performance and creativity. Then, in latter stages of the eating disorder when the individual is exposed to chronic hunger these traits begin to suffer (Hebebranda et al., 2003).

No significant differences in excessive exercising could be found between anorectic and bulimic patients, however the extent of excessive physical activity correlates with the rate of obsessional and perfectionistic traits (Shroff et al., 2006).

High physical activity level observations are not only a result of subjective reports by affected patients, but also by expert interpretation of questionnaires, measurements with pedometers, and rating scales. And these data suggest abnormal high activity levels in 31%-80% of AN patients (Holtkamp et al., 2005; Hebebranda et al., 2003). In a group of 297 purging bulimic females 20% were identified engaging in excessive exercising, for example more than 3 hours a day (Shroff et al., 2006).

This high variance in prevalence is due to the different approach on the definition of "hyperactivity" and thus differences in the collected data.

Historically, one can furthermore date back the observation of increased physical activity to Ernest-Charles Lasègue in 1873, as he described emaciated patients with an "increased aptitude for movement" (Casper, 2006).

A consistent finding in regards to energy expenditure in anorectic patients is the low resting metabolic rate, but without any signs of reduced total daily energy expenditure compared to healthy controls and bulimics. This is also explained by the increased physical activity with thus higher energy expenditure (Casper, 2006; Hebebranda et al., 2003). In bulimic patients, a certain conclusion is not possible, as findings from studies support lower as well as higher metabolic rates at baseline in the acute phase of the illness (de Zwaan et al., 2001).

Compulsivity regarding physical activity is in itself not an indicator for the presence of an eating disorder, however compulsive exercise is a trait linked to bulimia nervosa. A high rate of physical activity doesn't automatically imply an association with disordered eating behaviour (Adkins et al, 2005).

According to a study performed in 2006 with the aim to correlate plasma leptin levels with physical activity, it was suggested that the degree of physical activity is age related, especially in adolescents with AN between 12 and 17 years of age. Furthermore, physical activity could not predict the outcome and course of the eating disorder during the time of the study (van Elburg et al., 2007).

In advanced stages of AN, patients often claim that their excessive physical activity lay beyond their control in a form of an obsessive behaviour (Hebebranda et al., 2003).

6.1.1.1. Systems involved in activity in anorexia nervosa

A possible "risk factor" for increased activity in anorexia nervosa patients may lie in childhood, if the affected patient claims to have been "more physically active" compared to their playmates. This occurs in 50% of anorexia nervosa patients, which is twice as often as healthy children of the same age (Hebebrand et al., 2007).

Enzymatic changes, such as a raise of catecholestrogens are hypothesized to influence activity levels in affected patients, as these enzymes inhibit the synthesis of catecholamines (Casper, 2006).

Another involvement regarding activity levels is suggested to be found in the corticotropin releasing hormone system (CRH system) as a part of the hypothalamic-pituitary-adrenal axis, because of the main finding in anorexia nervosa patients of elevated CRH plasma levels as well as increased plasma and CSF cortisol levels (Hebebranda et al., 2003; Zandian et al., 2007). CRH is supposed to be involved in appetite suppression and in a rat model CSF injection of CRH showed a dose dependent increase in activity, which is consistent with the finding of the increased physical activity behaviour in anorexic patients (Casper, 2006).

Cortisol also has a very important influence on hyperactivity. It's thought to interact via the dopaminergic and noradrenergic system in cooperation with mesolimibic neurons and cells from the locus coerulus, areas which are the responsible for reward and attention (Zandian et al., 2007). This could contribute to maintaining the anorectic behaviour (Hebebranda et al., 2003).

The system involving the thyroid and its hormones is down-regulated in anorectic patients but paradoxically doesn't lead to reduction in physical activity. Casper summarizes this as it "highlights the pathological aspects of the drive for movement and alertness" in this patient group (Casper, 2006).

6.1.2. The role of leptin in anorexia nervosa and bulimia nervosa

Hyperactivity and food restriction are the core symptoms of anorexia nervosa. The very often observed exaggerated activity level in AN patients may have its origin in the rapid decline in leptin secretion at weight loss (Exner et al., 2000; Hillebrand et al., 2005). Animal studies have often demonstrated the attenuating effect of leptin on activity and lead us to believe in similar effects in humans (Exner et al., 2000; Hillebrand et al., 2005). Serum levels of leptin correlate very strongly with the amount of body fat and with body mass index (Hebebranda et al., 2003).

That humans are possibly equally affected by these interactions is displayed by subjective reports on the level of restlessness in AN patients which are highest when leptin levels and body weight are at their lowest (Hebebranda et al., 2005).

Holtkamp et al (2003) established a mean leptin concentration of 1.33 +- 0.76 ng/mL at an average BMI of 15.2 +- 1.6kg/m² and a total body fat of 11.1% +- 3.2% from a study

performed with 26 females diagnosed with AN according to the DSM-IV classification. These numbers underline the consistent findings of significantly reduced leptin levels in AN compared to healthy controls (Blüher et al., 2004) and furthermore point out another important implication of leptin in AN: Hebebrand mentions a threshold level of leptin of 2ng/mL as the initiation point of the down-regulation of the hypothalamic-pituitary-gonadal axis, thus possibly leading to amenorrhea, (Hebebrand et al., 2007) which usually occurs at approximately 70% of the mean weight of same aged healthy controls (Blüher et al., 2004).

Concerning the leptin serum levels of bulimic patients, a precise conclusion can't be made, as diverse results arose from different trials. Calandra et al (2003) presented leptin serum levels from 10 bulimic patients (BMI: 21.8+-2.3 kg/m²) aged 14-35 years (mean 23 +- 5 years) as high as 25ng/mL and exceeding those of 12 healthy overweight females (BMI 26+-2.8 kg/m²) with an average serum leptin level of 21.3 ng/mL (Calandra et al., 2003). However, these numbers do not represent the often documented significant correlation between BMI and plasma leptin levels (Monteleone et al., 2000) and should therefore be viewed sceptically. Monteleone (2000) presents 32 bulimic patients with a significantly reduced plasma leptin level compared to healthy controls. Leptin values ranged from 3.16 +- 1.6 ng/mL in amenorrhoic or oliogemorrhoic bulimics to 6.1 +- 4.8 ng/mL in normally menstruating bulimic females (Monteleone et al., 2000).

Further evidence for an involvement of leptin in the development of hyperactivity in anorectic patients was found in the study by Holtkamp and colleagues (2003), in which the high level of physical activity measured with accelerometers was correlated with low serum levels of the adipocyte derived hormone (Holtkamp et al., 2003).

A careful interpretation of findings in human subjects treated for AN suggest a threshold BMI starting at the 25th percentile for the attenuating effect of leptin on physical activity (Exner et al., 2000).

As with patients diagnosed with AN, bulimic patients also show significantly decreased serum leptin levels compared to controls. The relationship between body weight, total body fat, and serum leptin levels are also evident in bulimic patients however, these values exceed those of anorectic patients (Monteleone et al., 2000).

Decreased serum leptin levels have been found in female and male patients equally (Blüher et al., 2004).

6.1.3. Treating hyperactivity in anorexia nervosa and bulimia nervosa

Findings based on research on semi-starved, hyperactive rats in which 4µg leptin was infused into the lateral ventricle for 5 days indicate a significant involvement of leptin in activity. The daily running-wheel-activity (RWA) in those rats was significantly reduced compared to their littermates without leptin infusion. Exner et al (2000) therefore suggest and underline the findings that decreased serum leptin levels are a major signal in triggering hyperactivity (Exner et al., 2000).

Exner et al (2000) also delivers an explanation for the involvement of leptin in the reduction of hyperactivity and sees its main focus set on two hormones. Neuropeptide Y, an orexigenic hormone, is inhibited by leptin as is the anorexigenic hormone corticotropin releasing factor (CRF) The latter mentioned hormone increases cortisol levels, hypothesized to respond to physical activity and states of starvation (Exner et al., 2000; Blüher et al., 2004).

Frequently described traits in anorexia nervosa are neurotic obsessions and compulsions (Davis et al., 1995; Gee et al., 1999), usually classified as obsessive compulsive disorders and have been connected positively with exercise frequency (Hebebranda et al., 2003) and may be a significant influence in the development of eating disorders (Davis et al., 1995). Therefore we can find here a further treatment option in AN regarding excessive activity levels. Neuroleptics and drugs interfering with the dopaminergic, the noradrenergic, and the serotinergic system are known to decrease physical activity. Furthermore, weight gain can be observed in the treatment with neuroleptics (Hebebranda et al., 2003).

Gee and colleagues (1999) presented a case study in which a 14 year old female anorectic athlete was treated with a selective serotonin reuptake inhibitor (SSRI) along with a cognitive behavioural therapy, after an unsuccessful treatment of AN solely for 18 months prior to the new therapy regimen. After 10 weeks 80% of her OCD symptoms had gone and her body weight rose from less than 43kg to 47.7kg and 4 months later reached an even higher value of 54.4kg, demonstrating the striking efficiency of this combined regimen (Gee et al., 1999).

Physical activity and starvation independently increase central serotonin turnover in humans. Moreover, physical activity shifts the ratio of competing large neutral amino acids to tryptophan in the brain in the favour of tryptophan thus leading to higher central serotonin level. Shroff et al (2006) describe this as a sort of "self medication" in this patient group (Shroff et al., 2006).

The extent of physical activity in AN and BN does not predict the outcome of treatment and the course of the disorder (van Elburg et al., 2007).

A possible problem especially in the initial stages of re-feeding is the very steep increase of serum leptin levels observed in anorectic patients, as the high level may reduce caloric intake, thus leading anew to weight loss (Hebebrand et al., 2007).
Further problems in the treatment of AN lie in the increase of resting energy expenditure observed during weight gain. This results in a need of higher caloric intake to maintain or even gain weight, thus a possible hurdle in the treatment of this already difficult to treat patient-group arises (de Zwaan et al., 2001).

6.2. Obesity, activity and leptin

6.2.1. Energy expenditure in obesity

A major contribution to the growing worldwide epidemic of overweight lies especially in the reduction of physical activity. The increase of energy intake with high-fat and high carbohydrate diets furthermore enhances the effect of low physical activity levels. A simple but impressive calculation emphasizes this statement: if the daily energy intake exceeds the energy expenditure by just 5%, body weight increases by 5kg in one year (Jéquier, 2002).

Obese people are believed to be seated on average 2.5 hours more a day than lean people and considering the findings, that being seated for an hour a day rather than being upright, energy expenditure is reduced significantly, resulting in a weight gain of approximately 6kg in just a year (Knecht et al., 2008). In children it could be shown, that reducing the amount of television viewed per day reduces obesity (Robinson, 1999).

However, despite these alarming calculations, especially in childhood, a positive daily energy balance is necessary for growth and development of the children, yet the needed excessive energy is low after infancy (Krebs et al., 2007).

The resting metabolic rate accounts for about 65%-75% of the daily energy expenditure of sedentary individuals, and obese children and adolescents appear to have higher absolute resting metabolic rates than lean controls. However, adjusted for fat-free-mass and fat-mass, no differences were found between the two groups, yet females showed lower values than males (Molnár et al., 1996).

I shall focus on two important pathological states involved with obesity. The first being leptin deficiency and the second leptin resistance.

6.2.2. Leptin deficiency involved in physiological systems

As observed in so called ob/ob mice, animals with genetically cut off leptin production, humans with undetectable circulating leptin levels show hyperphagia due to an inability to experience satiety and thus increased body weight (Farooqui et al., 2002; Knecht et al., 2008). A reason for the lack of leptin is found in a rare frameshift mutation, as reported in three adipose children (Farooqui et al., 2002).

The consequences of the missing serum leptin cover a wide range of clinical implications which are all reversible upon external leptin administration. As previously mentioned hyperphagia and obesity are the main symptoms characterizing leptin deficiency. However, other hormones and their regulatory systems are also consistently affected in ob/ob. These could be an impaired hypothalamo-pituitary-thyroid axis regulation, hypogonadotropic hypogonadism, or high levels of circulating glucocorticoids, and one suspects these impairments also to be found in humans (Farooqui et al., 2002). The three children in the interesting study conducted by Farooqui and colleagues (2002) showed decreased free thyroxine (fT4) and tri-iodothyroine (fT3) levels and hyperinsulinemia with normal fasting glucose levels. Over time, insulin resistance could develop out of hyperinsulinemia thus leading to glucose intolerance and an increased risk for diabetes mellitus (Niswander et al., 2007).

Another very interesting involvement of leptin seems to lie in the regulation of some immune-system functions. Especially the proliferation of lymphocytes and their cytokine production seems to be inhibited by the absence of leptin (Baratta, 2002; Farooqi et al., 2002).

Centrally, leptin deficiency may lead to an increased expression of hypothalamic leptin receptors. This could be the reason why sub-physiological concentrations of serum leptin of just 10% of the predicted serum leptin concentration (0.01 mg/kg lean body mass) already cause anorectic effects in leptin deficient individuals (Farooqi et al., 2002).

Farooqi (2002) also mentions an increased bone maturation by a mean of 2.1 years in obese children compared to age equivalent children (Farooqi et al., 2002).

6.2.3. Leptin treatment in leptin deficient patients

As mentioned, it is hypothesized that in leptin deficient patients, hypothalamic leptin receptors are over-expressed, thus leading to an increased susceptibility of leptin when administered exogenously. Very impressive observations were made in the study performed by Farooqi et al (2002) in which three obese children identified with a frameshift mutation of the ob-gene encoding for leptin, were treated with subcutaneous injections of human recombinant leptin in levels ranging from sub-physiological concentrations up to supra-physiological concentrations. In summary the effects were:

- Marked reduction in total body weight, whereby 98% accounted for a reduction in body fat mass
- Increased lean body mass
- An energy intake reduction of up to 84% measured in an ad-libidum test meal as a result of the reduced hyperphagia
- Improved plasma insulin concentrations. These were reduced consistently over time during the therapy with recombinant human leptin as were serum cholesterol, triglycerides and LDL cholesterol levels. Furthermore, HDL cholesterol concentrations were increased in the all the observed children.

6.2.4. Possible leptin resistance as a result of diet induced obesity

As previously described, leptin acts as a satiety signal in the hypothalamus and furthermore interacts with a wide range of neuropeptides involved in appetite regulation (Leshan et al., 2006; Neary et al., 2004).

So why doesn't leptin inhibit food intake in obese individuals?

Serum leptin levels correlate significantly with total body fat (Paracchini et al., 2005) and therefore it's not surprising to find elevated leptin levels in diet induced obesity (Jéquier, 2002). However, the normal functions of leptin, such as reducing food intake or promoting energy expenditure are attenuated, probably due to the development of a resistance against leptin (Jéquier, 2002) Several mechanisms underlying this observation are discussed.

Probably the most significant reason for a leptin resistance is found in the short form of leptin receptors situated at the blood-brain barrier. These have been found to be less efficient in obese individuals (Jéquier, 2002). The leptin resistance is believed to only affect the metabolic regulatory mechanisms of leptin and not further features such as the sympathetic activation, leading to *selective leptin resistance* (Lima de Gusamo Correia et al., 2004).

Another reason for leptin resistance is the threshold level at which the blood brain barrier leptin receptors stop promoting the leptin effects to the CNS. Plasma leptin levels exceeding 25 ng/mL do not result in an increase of CSF leptin concentrations and thus do not enhance the expected leptin effects, like reduced appetite. Down-regulation of leptin transporters may also contribute to the development of leptin resistance, as the STAT3 activation in the hypothalamus and their intracellular signalling cascade promoted through leptin are attenuated in obese individuals (Jéquier, 2002).

6.2.5. Leptin treatment in diet induced obesity

In striking contrast to leptin deficient individuals, only leptin infusions at supra-physiological levels were able to produce the weight reducing effect in this second category of obese patients (Farooqi et al., 2002).

At the time of detection of the adipocyte derived hormone leptin in 1994 (Moschos et al., 2002; Baratta, 2002) hope was great to have found a potent therapeutic measure against obesity. However, after detecting that obese individuals do not respond to leptin as expected (reduced appetite, loss of body weight) due to a reversible resistance against leptin, the focus was set on other methods on obesity therapy (Shapiro et al., 2008).

Leptin alone, especially in the state of leptin-resistance, is not able to invoke the expected effects. However, combined with physical activity, the progress in weight loss is substantially higher than it would be with physical activity alone. This is the result of a

study on diet induced obese mice – hence mice with leptin resistance – performed by Shapiro and colleagues (2008). An explanation of leptin resistance can also be approached from the view of evolution. Because if leptin had evolved to prevent obesity, then leptin resistance wouldn't permit this natural regulatory effect and would furthermore limit the uptake of energy reserves in times of abundant food supplies in preparation of possibly food limited times (Jéquier, 2002).

6.3. Leptin, activity and ADHD

Motor behaviour is essentially influenced in children diagnosed with ADHD. In all subtypes of ADHD, the predominantly inattentive, predominantly hyperactive-impulsive, and the combined subtype, motor skills are drastically below average, and the severity of the inattentive symptoms in ADHD is positively linked to the degree of motor coordination difficulties (Tseng et al., 2004). Frequently found motor impairment categorized as fine motor skills affects handwriting skills, and fine motor skills are too significantly associated with the degree of ADHD pathology (Piek et al., 1999).

As far as I can conclude from my research on PUBMED, only a single study has tried to link leptin with ADHD, focusing hereby particularly on the effects of therapy with methylphenidate (MPH) on serum leptin levels. Iseri and colleagues (2007) state, that short-acting MPH in a daily dose of 0.6mg/kg neither influenced serum leptin levels nor did it lead to appetite suppression, a commonly seen side effect in a MPH treatment regimen (Iseri et al., 2007).

7. Study results

7.1. Subjects

Data were collected from 10 children between the ages of 8 and 18 years, who were being treated for anorexia nervosa, attention deficit hyperactivity disorder, and obesity. These children were treated on the psychosomatic ward of the children's hospital in Graz. 6 girls and 4 boys participated in the examination. We had 4 anorectic girls, five children with ADHD, and an obese female teenager.

Body weight ranged from 23kg to 146.5kg and body height from 1.24m to 1.66m, hence the BMI ranged from 14.7kg/m² to 53.8kg/m², lowest values detected in an anorectic girl and the highest, not surprisingly, in the obese female.

However, many problems arose during the period of the study regarding the compliance of the children, resulting in very scarce data.

7.2. Methods

7.2.1. Assessment of physical activity

Information on the daily physical activity was collected using two different methods. First of all, an activity questionnaire had to be filled out by the probands to obtain a subjective point of view on the amount of daily activity.

The data from the questionnaire, a combination of "A short questionnaire for the measurement of habitual physical activity in epidemiological studies" by Baecke et al (1982), the "International Physical Activity Questionnaire (IPAQ)", and a question concerning the "inner restlessness" of the probands.

To complete the data from the questionnaires, accelerometers were used to assess an objective view on the subject's daily activity by measuring the step count.

7.2.2. Blood sampling

Blood sampling occurred on referral of the children onto the psychosomatic ward. Originally, two further blood samples taken once a month were planned however, despite initial consent, the children were not willing to undergo further blood sampling. Therefore only referral blood sample values were obtainable.

7.2.3. Measurement of subcutaneous adipose tissue topography (SAT-Top)

The thickness of SAT layers was measured by the "Lipometer" (EU. Pat. No. 0516251) at 15 anatomically well defined body sites from 1-neck to 15-calf on the right side of the body. The measurement cycle takes about 2 minutes, during which the subject is standing. Lipometer results are interpreted as a percentage of body fat and can furthermore be used to define distribution types among obese or normal weight probands.

7.3. Results

7.3.1. Leptin

Leptin values ranged from 0.1 ng/mL in a 13 year old anorectic girl with a BMI of 17.3kg/m² to 11 ng/mL in the obese female teenager. Leptin values were only available from 8 children, 2 ADHD children were unavailable for blood samples.

7.3.2. Activity

Three patients, two ADHD affected boys and an anorectic girl, were assisted in filling out the combined activity questionnaire. MET levels (metabolic equivalent levels), sports-index and leisure-time index were then calculated. MET levels calculated for one of the boys with ADHD were 1746 MET-minutes/week, a total of 3154 MET-minutes/week summed up for the second ADHD child, and 3910 MET-minutes/week were determined in the anorectic girl, who described an increase of sports-activities as one of her methods to achieve weight loss. Sports-index ranged from 3 to 3.5, leisure-time index from 3.33 to 3.67.

The accelerometers were carried by three children. Yet again, compliance difficulties didn't allow us to retrieve more values than these. From the expected 72 hour period in which the devices should have been carried, data from only 12 to 17 hours carrying-time were actually obtained. Activity levels are represented by steps made within a certain time. These were 915 in 13 hours, 9892 steps in 12 hours in two anorectic patients, and 12087 steps in 17 hours in one of the male ADHD patients.

7.3.3. SAT results

Body fat measurements were carried out on three children aged 8, 11 and 13 years. Two ADHD boys were measured and an anorectic girl. Total body fat percentages ranged from 7.3% to 23.4%.

7.4. Patient examples

7.4.1. Anorexia nervosa

An eleven year old girl stated upon referral to the children's hospital an increase in physical activity with simultaneously reduced caloric intake. At the beginning of her disorder, she had started to reject food now and then, but then she had become preoccupied with food and her body weight and reduced her weight down to 43kg, which meant a total loss of 6kg compared to her previous body weight. At referral she suffered from shakiness and heavy sweating.

Her leptin levels were below 1 ng/mL, a value to be expected in states of emaciation, as in this case. Furthermore, her total body fat, measured with the "Lipometer", made up only 7.3% of her total body weight.

Considering the frequently stated correlation between body fat mass, BMI and leptin levels (Jéquier, 2002; Paracchini et al., 2005), we find in this girl a "classic" example for this relationship. Her BMI of 15.4 kg/m² lies below the 25th percentile for her age (Kuczmarski et al., 2000), her serum leptin level is below the range considered as normal (usually between 2ng/mL and 10ng/mL (Baratta, 2002)) and her total body fat of 7.3% further underlines the reduced leptin production displayed by a diminished production site.

In this eleven year old girl, another possible influence of leptin appears to be evident. Low leptin levels, hence a state of emaciation, are considered as a driving force for physical activity (Hebebranda et al., 2003). Comparing her step count with that of the second anorectic girl, who hasn't stated an increase of physical activity in the past, we find a nearly 12-fold increase in the values (824 steps/hour vs. 71 steps/hour). Concerning activity, with 3910 MET-minutes/week she had the highest MET-level score of the three children who filled out the activity-questionnaires. Furthermore, she stated that she started with rope skipping for about half an hour per day, since she had become preoccupied with her body weight and eating behaviour.

My experience on the psychosomatic ward showed me how difficult it can be to treat this patient group. In this special case for example, I had the feeling that her ambivalent view on her own body and the general reluctance towards treatment was the reason for her unwillingness to undergo further examinations.

7.4.2. Adipositas

The only case of adipositas in our study was represented by an 18 year old female. Her parents and her three brothers also struggle with overweight, implicating a strong social factor for her weight problem. Her intense war against her body weight has a long history of ups and downs. Past weight reduction programs, such as a 5 week summer-camp, resulted in a very short term weight loss of 10kg. At referral, she once again had gained weight. Even her parents were now concerned, that her increased body weight may prevent her from living adulthood without mental and physical pain.

It is not difficult to see, that the 146kg body weight she carries also weighs heavily on her mental wellbeing, explaining her aggression towards me and the staff in the hospital making it very difficult to treat her.

With a height of 1.65m and a weight of 146kg, her BMI of 53.8kg/m² lay way over the 97th percentile for age and gender (Kuczmarski et al., 2000).

Surprisingly, her serum leptin level of 11 ng/mL isn't as skyrocketing as one would expect, although this value does lie in the range of 10 ng/mL to 100 ng/mL serum leptin in obese females stated by Baratta (2002). The question arises, as to when, at what time of day, the blood sample was taken, as leptin is secreted in a pulsatile manner (Trayhurn et al., 1999). Therefore, a single leptin value without specification of the time of sampling is not easy to interpret.

Although she gained weight whenever she stayed at home for several days, fortunately, the hospital treatment did generally show positive results. At the time the study ended she had lost approximately 20kg, which meant her BMI had gone down to 45.9 kg/m², still exceeding the 97th percentile by a long way, however.

Despite the fact that the treatment showed good results, she was unwilling to further participate in my study. I had the feeling, and her calling me a "child" supports me in this statement, that the absence of a "Dr."-title, made it difficult for her to follow my programme. Obviously, she only follows when she is confronted with a rigorous, venerated person.

7.4.3. ADHD

A thirteen year old boy, with a body weight of 54.9kg and a height of 1.57m (50^{th} percentile) represents a slightly overweight individual of normal body size (BMI = 22.3kg/m²; $>85^{th}$ percentile for age and gender) (Kuczmarski et al., 2000). His total body fat, measured with the lipometer was as high as 23.3%.

His step count per hour was 711, measured over a period of 17 hours. This value is slightly lower than the one found in the 11 year old anorectic girl. However, looking at the activity questionnaire, all the activity in the young man comes from leisure time activities, as he doesn't state any special sports activities like running, cycling, team sports or such.

Sadly, no leptin values were gathered in this individual, as it would have been interesting to see, if he had in fact low leptin levels implicating the high grade of activity, despite the high amount of body fat, which would actually lead to increased leptin levels.

The second subject, a 10 year old boy had a total body weight of 38kg and a height of 1.46m resulting in a BMI value just above the 50^{th} percentile of 17.8kg/m² (Kuczmarski et al., 2000). He had a serum leptin level of 7.4ng/ml.

Working with this child (in fact with all ADHD patients) was very pleasant, because they were very active (not surprisingly) and cooperative and we progressed quickly. However a similar problem regarding the compliance in this patient group arose, but it affected the parents rather than the children. ADHD patients are outpatients, only on the ward at the time of referral and approximately for a week for initial therapy. Despite my efforts in arranging meetings with the children by phone-contact with the parents, appointments were not kept, due to diverse reasons such as conflicts with working time, the great distance to Graz, or holidays.

7.4.4. The Children Strike Back

After several weeks I realised the first problems in obtaining data for my study. The exhausting therapy made it difficult for the children to understand the necessity for further study with even more examinations. And furthermore, I was not capable of explaining the importance of the study, mainly, I suppose, because of my status of "just a student". This enhanced their reluctance to participate in the trail, despite their initial consent.

Finally, after several attempts to find a solution with the children (for example I arranged a group talk with all participating kids) and after my effort to improve the situation with the help of the nurses and the case doctors, I had to accept, that it wasn't going to be possible to gather further information. During the final talks with the children, I was told by them, that they had decided not to participate any further in the study. As a reason for this they mentioned a passage from the consent form, which allowed them to drop out of the study whenever they wanted without having to give a reason. Like the domino effect, one child dropped after the other. They also told me, that they just don't feel like taking part in the study.

I just had to accept that.

Although I knew it would be difficult to work with children and especially teenagers, I had never expected the magnitude of problems I would encounter in teenagers suffering from eating discords.

Personally I hope, that all affected girls and boys can master their difficulties and it all finds a happy conclusion.

8. Abbreviations

AN	Anorexia nervosa
5-HIAA	5-hydroxyidolacetic acid
5-HT	5-hydroxytryptamine
ADHD	attention deficit hyperactivity disorder
AgRP	agouti related peptide
Alpha-MSH	alpha-melanocortin stimulating hormone
AR	attributable risk
ARC	arcuate nucleus
BDNF	brain derived neurotrophic factor
BMI	body mass index
BN	Bulimia nervosa
CCK	cholecystokinin
CNS	central nervous system
CRF	corticotropin releasing factor
CRH	corticotropin –releasing hormone
CSF	cerebro-spinal fluid
DMII	diabetes mellitus type 2
DNA	deoxyribonucleic acid
DSM-IV	Diagnostical and Statistical Manual of the American Psychiatric Association 4^{th} edition
EA	exendin amide
EENPP1	ectoenzyme nucleotide pyrophosphate phosphodiesterase
FSH	follicle stimulating hormone
fT3	free tri-iodothyroine

fT4	free thyroxine
GH	growth hormone
GHRH	growth hormone releasing hormone
GHS-R	growth hormone secretagogue receptor
GLP-1	glucagon like peptide 1
GnRH	gonadotropin releasing hormone
GNRH1	gonadotropin-releasing-hormone 1
HDL	high density lipoprotein
HKD	hyperkinetic disorder
HPA	hypothalamic-pituitary-adrenal
HPG	hypothalamic-pituitary-gonadal
ICD-10	International Classification of Diseases, 10th edition
IL-6	interleukin 6
JAK	janus kinase
LDL	low density lipoprotein
LEPRl	long form leptin receptor
LEPRs	short form leptin receptor
LH	luteinizing hormone
LHRH	luteinizing hormone releasing hormone
MC	melanocortin receptor
MET	metabolic equivalent
mRNA	messenger ribonucleic acid
MS	metabolic syndrome
NO	nitric oxide
NPY	neuropeptide Y
Ob-R	leptin receptor

ObRb	long form leptin receptor
OCD	obsessive compulsive disorder
OR	odds ratio
POMC	pro-opiomelanocortin
PP	pancreatic peptide
PVN	paraventricular nucleus
PYY	Peptide YY
RSNA	renal sympathetic nerval activation
RT-PCR	reverse transcription polymerase chain reaction
RWA	running wheel activity
SAT	subcutaneous adipose tissue
SH2	Src homology 2 domain
Src	a gene
SSRI	selective serotonin reuptake inhibitor
STAT	Signal Transducers and Activators of Transcription
TRH	thyrotropin-releasing hormone
WHO	World Health Organisation

9. Tables and diagrams

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Appendix

Curriculum vitae

Gunther Gores

Persönliche Daten

Geboren am 3. Januar 1982 in St. Georgen an der Stiefing, Österreich

Deutscher Staatsbürger

Gesprochene Sprachen: Deutsch, Englisch, Spanisch

Schulische Ausbildung

1989 – 1990: 1. und 2. Klasse der VS Leibnitz

1990 – 1993: 3., 4. und 5. Klasse der Deutschen Schule Jeddah, Saudi Arabien

1993 – 1996: 2. bis 4. Klasse Unterstufe des Bundesrealgymnasiums Leibnitz

1996 – 2001: HTBLA Kaindorf für EDV und Organisation; Maturaabschluss mit ausgezeichnetem Erfolg

Studium

2002 – 2008: Studium an der Medizinischen Universität Graz

Auslandsaufenthalte

September 2001 bis September 2002: Asturias, Spanien

Interessen und Hobbies

Triathlon, Fußball, Tennis

Lesen

Programmieren

Schlagzeug und Musik