Bariatric pediatric surgery

Protocol

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Presented

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CHAPTER I

INTRODUCTION

Scope and epidemiology:

No child chooses to become obese; the quality of life of an obese child is similar to that of a child receiving cancer chemotherapy. The discovery of leptin in 1994 revealed a complex neuroendocrine axis regulating energy balance (1).

Obesity is increasing dramatically worldwide and in year 2013, 43 million children under the age 5 were overweight/ obese and this figure expected to reach 60 million by the year 2020. Many of the obese children and adolescents now will become future's obese adults. The tracking of childhood obesity into adulthood depends on several parameters as age, the presence of parental obesity and severity of obesity (2).

The epidemic of obesity is attributed to recent changes in the environment (easy access to high energy palatable food, combined with a decreased physical activity), whereas individual differences in obesity risk are attributed to genetic differences between individuals: the heritability of body mass index (BMI) has been estimated to approximate 70% in adults and is even higher (77%) for younger people raised in an increasingly obesogenic environment (3).

In Egypt, there is increase in the prevalence of obesity in boys and girls from 23.4% and 29.7% in 2005 to 35.6% and 32.8% respectively, with a percent increase of 52.13% in boys and 10.43% in girls (Fig. 1) (4).

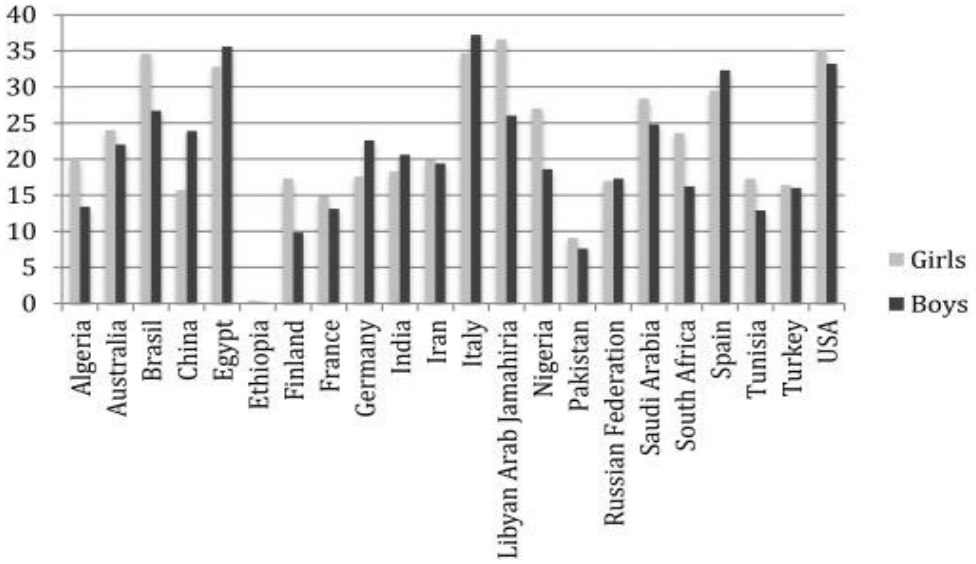

Fig.1 The prevalence of childhood overweight and obesity in various countries in the world (4).

Obesity is a complex and multifactorial disease involving an interaction between genetics, regulation of energy balance, and strong environmental and behavioural influences such as increased caloric intake and decreased physical activity in today's modern society. The interplay among these variables is important to understand the development and increased prevalence of childhood obesity. It has been advocated that when genetically pre-disposed individuals are placed in an adverse environment obesity occurs (5).

Childhood obesity can lead to a variety of preventable health hazard that affect different systems of the body including orthopedic, cardiovascular, metabolic, endocrine, psychosocial, dermatological, neurological and renal systems. The best approach to this condition is to prevent the abnormal weight gain. Several strategies for prevention are presented (6).

In addition to prevention, the American Academy of Pediatrics (AAP) recommends a four step approach for the

management of childhood and adolescent overweight and obesity, the first two of which are dietary and lifestyle interventions of escalating intensity. If there is insufficient progress and outcome after three to six months, these guidelines recommend advancing to more effective stages, such as medication or surgery, and referral to obesity management experts for specialized interventions (7).

Current non-surgical management for extreme obesity in adults and children seldom result in the significant, durable weight loss that can improve the health outcomes, and any benefit gained is often reversed when they have been stopped. In addition, non-surgical management may be less effective in those with higher BMI and more co-morbidities. This prompts for a search for more effective measures. Bariatric surgery has been introduced as an intervention for those with extreme obesity (8, 9).

The three main surgical options for adolescents at present include (10, 11):

1. Laparoscopic sleeve gastrectomy (LSG):
   >60 percent of total performed surgeries.

2. Roux-en-Y gastric bypass (RYGB):
   <30 percent of total performed surgeries.

3. Laparoscopic adjustable gastric banding (LAGB):
   <5 percent of total performed surgeries.

AIM OF THE WORK

This study aims at reviewing the pediatric obesity with the emphasis of the bariatric surgery as an effective measure for its treatment in the current literature, and to assess the outcomes and complications of different bariatric procedures.

CHAPTER II

ETIOLOGY AND PATHOPHSIOLOGY OF PEDIATRIC OBESITY

II.1. PHYSIOLOGY AND PATHOPHYSIOLOGY:

The Neuroendocrine Control of Energy Balance:

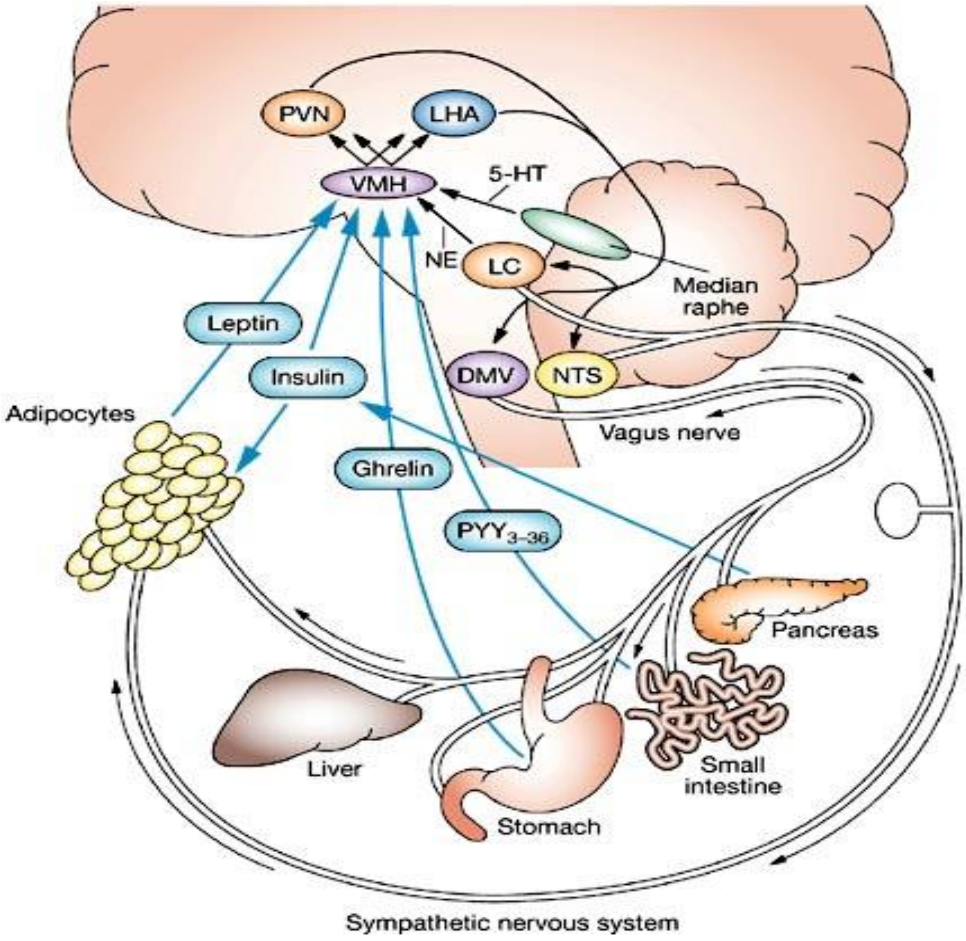

Fig.2 The homeostatic pathway of energy balance (12).

The neuroendocrine axis is composed of three arms *(Fig.2) (13, 14)*

A. *The afferent arm:* sends peripheral information on hunger and peripheral metabolism (in the form of hormonal and neural inputs) to the hypothalamus.
B. *The central processing unit:* within the hypothalamus. These include:
    1. The ventromedial hypothalamus (VMH); consisting of the ventromedial (VMN) and arcuate (ARC) nuclei), which receives afferent peripheral signals as well as other central stimuli.
    2. The paraventricular nuclei (PVN) and lateral hypothalamic area (LHA), act as a doorway neurotransmitter system to alter neural signals for changes in feeding and energy expenditure.
C. *The efferent arm of autonomic effectors:* originates in the locus coeruleus (LC) and dorsal motor nucleus of the vagus (DMV), which regulate energy intake, expenditure, and storage.

Genetic or metabolic alterations or anatomic disruptions of the neuroendocrine axis can alter energy intake or expenditure, leading to either obesity or cachexia (13).

A. The afferent system:

It has three components:

1. Alimentary Afferents That Promote Hunger:

a) The afferent vagus (13)*:* It is the primary neural connection between the brain and the gut. It sends information regarding mechanical stretch of the stomach and duodenum and gastric fullness to the nucleus tractus solitarius (NTS).

b) *Ghrelin "Hunger hormone"* (14, 15)*:* An octanoylated 28-amino acid peptide. Its endogenous secretion from the stomach is high during fasting and decreased by nutrient administration and its plasma levels are low in most obese individuals, suggesting that ghrelin is a response to, rather than a cause of, obesity, also its infusion increases food intake.

It binds to the ghrelin receptor/ growth hormone secretagogue receptor (GHS-R) in:

i. The VMH thus increasing hunger, food intake, and fat deposition and triggering meal initiation.
ii. The pituitary gland inducing growth hormone (GH) release.

2. Alimentary Afferents That Promote Satiety:

a) *Peptide YY3–36 (PYY3–36)* (16)*:* It is a gastrointestinal signal to control meal volume. It is secreted by intestinal L-cells following exposure to nutrients promoting satiety. It crosses the blood–brain barrier and binds to the Y2 receptor in the VMH reducing neuropeptide Y (NPY) mRNA in neurons of the orexigenic arm of the central processing unit. Although the pharmacology of this peptide is being elucidated, and agonists are being developed, its specific role in obesity is not yet known.

b) *Glucagon-like peptide-1 (GLP-1)* (17, 18)*:* It is produced by the intestinal L-cells from the

preproglucagon molecule. It reduces food intake by:

i. Reducing gastric emptying, by direct effect on the stomach.
ii. Reducing corticotropin-releasing hormone (CRH) signaling in the PVN.
iii. Increasing leptin signaling in the VMH.

It stimulates β-cell replication and activation leading to:

i. cAMP production.
ii. Protein kinase A activation.
iii. Insulin secretion and thereby improves glucose tolerance in patients with type 2 diabetes.

c) Cholecystokinin (CCK) (19)*:* An 8-amino acid gut peptide released in response to a caloric load. It circulates and binds to CCKA receptors in the pylorus, vagus nerve, NTS, and area postrema to promote satiety.

3. Metabolic Afferents Controlling Energy Balance:

a) Leptin (20, 21, 22)*:* The balance of energy intake and expenditure is normally regulated very tightly by the hormone leptin. It is a 167-amino acid hormone that is produced by white adipocytes. Its primary neuroendocrine role is to mediate information about the size of peripheral adipocyte energy stores to the VMH. It reduces food intake and increases the activity of the sympathetic nervous system (SNS). Low leptin levels indicate diminished energy stores, which

impact on the VMH to increase food intake and reduce energy expenditure as in those with lipodystrophy syndromes and anorexia nervosa. It is a prerequisite signal to the VMH for the initiation of high-energy processes such as puberty and pregnancy. In the fed state, circulating levels of leptin correlate with percent body fat**.**

When binding to its VMH receptor, three neuronal signals are transduced:

- *First:* the opening of an ATP-sensitive potassium channel, which hyperpolarizes the neuron and decreases its firing rate.
- *Second:* the activation of a cytoplasmic Janus kinase 2 (JAK2), which phosphorylates a tyrosine moiety on proteins called signal transduction and transcription (STAT-3).The phosphorylated STAT-3 translocates to the nucleus, where it promotes leptin-dependent gene transcription.
- *Third:* leptin activates the insulin receptor substrate 2/phosphatidylinositol-3-kinase (IRS2/PI3K) second messenger system in ARC neurons, which increases neurotransmission of the central anorexigenic signaling pathway.

b) *Insulin* (23) *:* It plays a critical role in energy balance by acting:

i. Peripherally:
   a. Promoting glycogenesis, muscle protein synthesis, and fat storage.

b. Regulates the production and action of neuroendocrine modulators of nutrient uptake and metabolism.

ii. Centrally: It is transported across the blood–brain barrier and binds to:

a. VMH neurons regulating food intake.

b. ARC neurons activating the IRS2/PI3K second messenger system which increases neurotransmission of the central anorexigenic signaling pathway.

B. Central processing:

This circuit consists of two arms:

1. Anorexigenesis (24)**:**

a) *Proopiomelanocortin (POMC):* Leptin stimulates the production of POMC, from some leptin-responsive hypothalamic neurons, which is the precursor for adrinocorticotrophic hormone (ACTH), alpha, beta and gamma melanocyte-stimulating hormone (MSH), beta-lipoprotein and beta-endorphin. Alpha-MSH binds to melanocortin 3 receptor (MC_3R) and melanocortin 4 receptor (MC_4R) in the ARC to regulate appetite and energy expenditure.

b) *Cocaine/amphetamine-regulated transcript (CART):* hypothalamic neuropeptide induced by leptin and reduced by fasting. Intrahypothalamic infusion blocks appetite,

while antagonism of endogenous CART increases caloric intake.

2. **Orexigenesis** (16,25)**:**

a) *NPY:* Its function within the hypothalamus includes initiation of feeding, puberty, and regulation of gonadotropin secretion and adrenal responsiveness by acting through Y1 and Y5 receptors. Fasting and weight loss increase NPY expression in the ARC, accounting for increased hunger, while PYY3–36 (through Y2 receptors) and leptin decrease NPY mRNA.

b) *Agouti-related peptide (AgRP):* It is an endogenous competitive antagonist of all MCR. In the presence of large amounts of AgRP at the synaptic cleft in the PVN, α-MSH cannot bind to the MC4R to induce satiety.

Ghrelin receptor immunoreactivity co-localizes with NPY and AgRP neurons, while insulin and leptin receptors are located on both POMC/CART and NPY/AgRP neurons in the VMH, suggesting divergent regulation of each arm (26).

C. The efferent system:

The MCRs in the PVN and LHA transduce signals arising from the VMH in order to modulate activity of:

1. **The Sympathetic Nervous System (SNS)** (27, 28)**:**
   - The SNS increases energy expenditure by activating lipolysis in white and brown

adipose tissue and promoting energy utilization in skeletal and cardiac muscle.

- Catecholamines binds to:
  - β2-adrenergic receptors in the muscles stimulating glycogenolysis, myocardial energy expenditure, increases in glucose and fatty acid oxidation and increases protein synthesis.
  - β3-adrenergic receptors in white and brown adipose tissue increases cAMP, which activates protein kinase A (PKA).
    - In white adipose PKA activates hormone-sensitive lipase, which generates ATP from hydrolysis of triglyceride.
    - In brown fat PKA phosphorylates cAMP response element-binding protein (CREB), which induces expression of peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α). PGC-1α in turn binds to the uncoupling protein-1 (UCP-1) promoter and increases its expression.

2. The Efferent Vagus and Energy Storage (29)**:**

As a result of declining levels of leptin and/or persistent orexigenic pressure, the LHA and PVN send efferent projections residing in the medial longitudinal fasciculus to the dorsal motor nucleus

of the vagus nerve (DMV), activating the efferent vagus.

The efferent vagus opposes the SNS by facilitating energy storage in four ways:

i. It decreases myocardial oxygen consumption by lowering the heart rate.
ii. It increases nutrient absorption by promoting GI peristalsis and pyloric opening.
iii. It increases insulin sensitivity by potentiating the uptake of glucose and FFA into adipose tissue.
iv. It increases postprandial insulin secretion, which increases fat deposition.

Other Neuroendocrine Modulators of Energy Balance:

(a) Norepinephrine (NE):

The actions of NE on food intake seem paradoxical, as intrahypothalamic NE infusions stimulate food intake through effects on central α2- and β-adrenergic receptors, while central infusion of α1-agonists markedly reduces food intake (30).

(b) Serotonin (5-HT):

The role of 5-HT in the transduction of the satiety signal may have both central and peripheral components, as intestinal 5-HT secreted into the blood stream during a meal may impact GI neuronal function and muscle tone while binding to 5-HT receptors in the NTS to promote satiety (31).

(c) Melanin-concentrating hormone (MCH):

It is important in behavioral responses to food such as anxiety and aggression. ICV administration of MCH