COMPLICATIONS OF OBESITY

Obesity is truly a whole-body problem. Any of the physiological systems can be compromised. The managing healthcare worker should consider problems beyond the obvious cardiorespiratory complications of hypercholesterolaemia, cardiac overload, hypertension, and respiratory difficulties. The higher the BMI, the more apparent the other complications in non-cardirospiratory systems will be. Other systems affected may include:

1. Musculoskeletal: osteoarthritis, muscle atrophy, osteopaenia, increased likelihood of injury.
2. Endocrine: Diabetes mellitus type 2, hypothyroidism, elevated cortisol.
3. Neurological: peripheral nerve damage, cognitive decline including dementias like Alzheimer's disease, mood disorders, insomnia, CVAs
4. Dermatological: skin infections and fragility, hyperpigmentation, psoriasis.
5. GIT: dysregulation of bowel activity, haemorrhoids, cholecystitis, fatty liver, pancreatic disease.
6. Neoplasia: obesity is associated with numerous cancers, some of which indicate a markedly increased risk, e.g., endometrial (5-7x). Others have a much smaller risk, e.g., gallbladder (1.6x) with many in between.
7. Psychosocial: social relationships are frequently compromised, & obese people report greater loneliness.

The most common organ systems impacted by obesity and their complications are summarised in Figure 2.

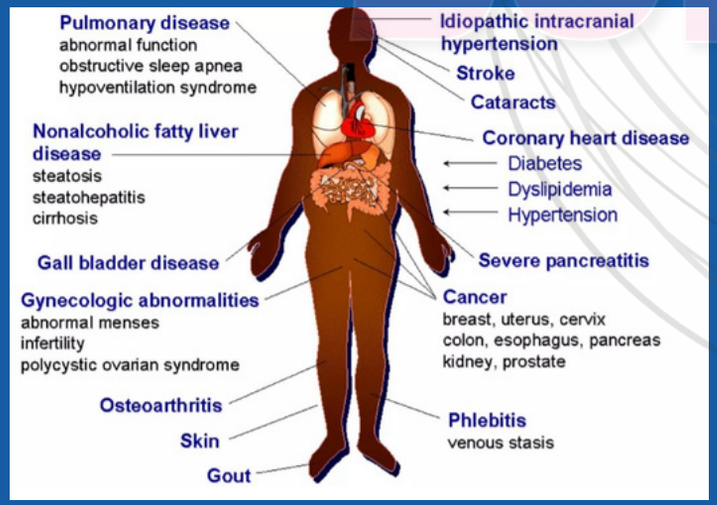

Figure 2. Common complications associated with diabetes (Credit: The Lancet, 2002; 360:475).

OBESITY MANAGEMENT

The correct management of obesity is far more complex than most healthcare workers realise. The first decision to make is whether obesity is primary. Is there a primary syndromic or non-syndromic cause? Is it helpful to do genetic testing or assess for endocrine causes, e.g., a primary Cushing's disease, Polycystic Ovarian Syndrome, etc.? Specific pharmacological intervention may be required.

Assuming obesity is secondary, the first point to be clear about is that it is a multifaceted physiological disorder that requires lifestyle changes. Labelling the problem as excessive energy intake and thus focusing purely on counting calories is almost certainly doomed to fail for the reasons discussed earlier. This may be helpful at a later stage, but at the beginning, appropriate dietary change is only one of many arms of the management strategy. It is just as important to focus on psychosocial factors, physical activity, endocrine dysregulation (thyroid, insulin, cortisol, and the hypothalamic-pituitary-gonadal axis), eating patterns, alcohol consumption, mood, sleeping, and much more. Certainly, it will not be able to pinpoint in most cases whether one of the system dysfunctions, say DM type 2, is a contributing cause or a consequence of obesity. By acknowledging that it is both, one is reminded that treating obesity as a multifaceted physiological disorder is the most appropriate strategy.

For the general practitioner, I would suggest the following basic pathology assay: U and E, Hb, CRP, LFTs, HbA1c, lipogram, TSH, fasting insulin, screen for PCOS (female), cortisol, and an ANF as a screen for an autoimmune condition. Depending on the clinical presentation, others may be required (e.g., co-existing suspicion of a urinary tract infection or something else), but these are the ones one may suggest at the outset. One may also consider severe disruption of the hypothalamic-pituitary-adrenal/gonadal axis and investigate appropriately.

Finally, it is worth noting that obesity management is a lifelong commitment. There will always be setbacks, which can be disheartening. However, educating healthcare workers on the nature of obesity as a lifelong condition with long-term objectives via small steps is a sensible approach. Furthermore, patients should actively be discouraged from falling prey to misinformation and fad diets. Misinformation is a huge problem in this field. Including the skills of a respected nutritionist/dietician will likely be money well spent.

Reference:
The following provides the most up to date review of obesity by the American Heart Association.
Clark JM, et al. Obesity and Overweight: Probing Causes, Consequences, and Novel Therapeutic Approaches Through the American Heart Association's Strategically Focused Research Network. J Am Heart Assoc. 2023 12:e027693.

clientservices@togalab.co.za **011 663 6300**

MAY 2024 | ISSUE 01

toga MOLECULAR BIOLOGY PATHOLOGY LABORATORY **LAB INSIDER**

OBESITY

DR PIERRE M. DURAND

Obesity has emerged as one of the most pressing health problems globally, especially over the last 50 years. It is set to have an even more significant impact on human health and economics in the coming decades. In this newsletter, I will cover some of the main topics in obesity like epidemiology, aetiology, energy balance and metabolism, complications, and finally some notes about management strategies. But first, why has obesity emerged as such a significant health issue?

THE ORIGINS OF OBESITY

Obesity is really a problem of the 20th and 21st centuries. It's usually said to have started in the 1970s, but that's only because the WHO declared it so based on the data at the time. But most non-communicable diseases don't have a 'point of origin'. Some recent data from a Danish study (SCIENCE ADVANCES, 2023, 9:37) push the epidemic back to before WW II, when it was noted that the heaviest people were already getting heavier. Whatever the timing, there are two main reasons for the rise in obesity. These are not the only reasons, but they seem the most important. First is the dietary influence, and second is the increase in sedentary lifestyles. The problem is greater consumption of energy-dense, processed foods in the former. In the latter, the kinds of occupations and leisure activities require less activity, and many social ills accompany lifestyle changes, e.g., stress, television, insomnia, mental health problems, etc. The two main factors (diet and lifestyle) form a positive feedback loop. The time constraints of a 'modern' lifestyle promote the consumption of convenience foods, and poor diets cause further lifestyle problems like inactivity, mental health issues and insomnia. If we trace the origins of the rapid rise in obesity, we can see that it correlates with these two primary factors: diet and lifestyle.

EPIDEMIOLOGY

Obesity is, well, a massive problem. WHO labels it a pandemic. Obesity is defined as an excess of body adiposity, but of course this is problematic. What does that mean for different groups of people? And then by quantifying the definition (usually in terms of BMI), one soon realises that these are simply best guesses. Still, they do have some uses, except that one must remember that the thresholds for obesity are not biologically the same for everyone. It is sometimes considered more helpful to look at the epidemiology of diseases that may be caused by obesity e.g., type II DM. But that is also not ideal. Either way, the evidence that obesity is a global issue is uncontroversial. In addition, the problem is worse in some communities than others. That is of course, due to both genetic and lifestyle/dietary factors.

If we use the definition of obesity as a BMI≥30 then according to the WHO one in eight people was obese in 2022. And worldwide adult obesity has more than doubled since 1990. Adolescent obesity has quadrupled. These statistics vary enormously. Consider that American Somoa has the highest prevalence (>70% of the population is defined as obese) and it seems Ethiopia has the lowest (1%). Of course one must treat these numbers with great scepticism. There was/is a famine in Ethiopia so trying to measure obesity in 'normal' circumstances sounds a bit silly. In South Africa, it is claimed by WHO that roughly 31% of men and 68% of women are obese. According to the definitions used they are likely close to the mark. But it does highlight two points. First, there is a tendency for poorer countries and groupings within populations to have higher rates of obesity. This relates to the causes of obesity being closely associated with poor diet and nutrition. And second, there are major differences in ethnicities that aren't usually taken into account. East Asians (Japanese for example) have lower BMIs based on genetics. Polynesians have some of the highest.

AETIOLOGY

The most important clinical decision to make is whether the cause of obesity is primary (organic) or secondary. There are numerous primary causes, the leading cause being something other than diet/lifestyle. Examples include:

1. Non-syndromic genetic causes, e.g., mutations and polymorphisms in leptin, melanocortin and other genes (see Int J Mol Sci. 2022, 23) and syndromic genetic causes, e.g., Prader–Willi, fragile X, etc.
2. Endocrine/metabolic conditions, e.g., hypothyroidism, Cushing's etc.
3. Iatrogenic causes, especially medications like corticosteroids, psychiatric drugs, and antiepileptics.
4. Psychiatric conditions, especially mood and eating disorders.
5. Musculoskeletal conditions that lead to chronic inactivity and associated dietary problems.

Secondary causes are sometimes divided into various contributing factors, but broadly speaking, they are usually related to the two main components of diet and lifestyle (Figure 1). It is worth pointing out that the genetics associated with secondary causes refer to how individuals respond to particular diets and lifestyles. This differs from the genetics that are causally related to the physiological abnormalities leading to obesity.

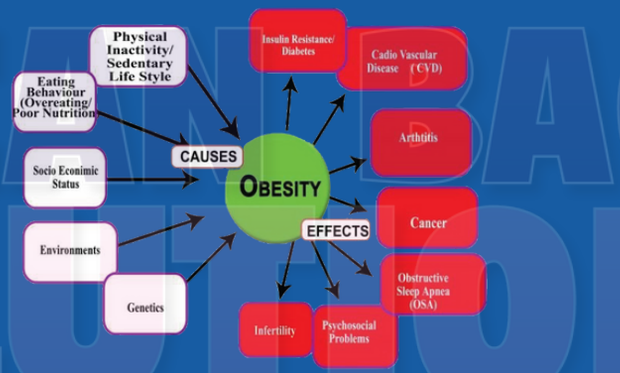

Figure 1. Causes and Effects of Obesity

ENERGY BALANCE & METABOLISM

Obesity is a disruption of metabolic homeostasis. The molecular pathology of obesity is exceedingly complex and to reduce it to one or two metabolic or endocrine pathways is hugely misleading (except of course for the well described genetic causes).

On some level, the dysregulation of most metabolic pathways, from protein metabolism to neuropeptides, from the hypothalamic-pituitary-adrenal/gonadal axes to the urea cycle, can be associated with obesity. The point is that there is seldom, if ever, a single metabolic cause of secondary obesity, and certainly, the effects of obesity permeate through the individual's entire physiology.

It is well established that obesity affects multiple systems, including endocrine, liver, musculoskeletal, cardiorespiratory, neurological (centrally & peripherally), reproductive, etc. In many discussions of energy balance and obesity, it is often said that obesity is caused by an imbalance in energy intake versus energy output. Well, that is only partially true. And I find that an unhelpful approach for two reasons. First, it focuses on the management approach of decreasing intake and increasing output. Doing so is notoriously problematic. It will eventually work, assuming the calculations are updated over the course of management, but almost all patients say that doing so only works in the short term. Long term, this seldom works. And that brings the second reason to the fore. One kJ of energy doesn't have a set equivalent body mass value. It depends on what is being weighed. One kilogram of muscle, one kilogram of adipose, and one kilogram of glycogen all have different chemical energy values. And the tissues also all have different resting metabolic rates. So, the input-output approach depends on what kind of energy is being consumed, which tissues are used to burn energy, and how the energy is stored in the body (protein, fat, or glycogen). This is something that the vast majority of non-obesity specialists are either unaware of or ignore. One might have a small energy deficit but gain weight. This is unlikely to happen at morbidly obese levels, but most patients using this energy balance strategy are in the overweight, mildly obese range.

Associated with the two problems above is the issue of changing metabolism. Human physiology has built-in homeostatic compensatory mechanisms. Physiological compensatory mechanisms are activated when diet suddenly changes or the energy balance shifts. This means that the weight being shed has a changing energy value because there is a change in the tissue type being catabolised. The upshot is that the original calculation of energy intake versus energy output is no longer valid.

There are other problems associated with this approach because the kind of energy that is being consumed influences the storage tissue that it is converted into. Covering all the problems associated with the energy input-energy output strategy is beyond the scope of this newsletter. The point I wish to make is that one doesn't have to ignore this metric, but don't make it the primary focus of weight loss.