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A renaissance for cardio-metabolic surgery:

Better outcomes and lower costs?

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Not too long ago surgeons routinely treated metabolic problems including hypertension, hyperlipidaemia and obesity. However, these areas declined as drug therapies became available and surgical approaches lost favour due to high rates of perceived complications. Surgery survived in specialist metabolic oncological applications for treatment of endocrine adenomas or carcinomas. Metabolic endocrine surgery has grown ever more sophisticated with better imaging, more sensitive sampling techniques, intra-operative endocrine monitoring using point-of-care assay technologies and the increasing use of minimal access and eventually robotic surgery techniques [1-3]. The diagnosis of primary hyperparathyroidism (PHPT) is more frequently made at a significantly earlier stage than in the past. Surgery is performed for both prognostic benefit and symptom relief. Surgical approaches have evolved rapidly in recent years with an evolution in minimally invasive procedures aided by improvements in preoperative localisation[4]. Day surgery procedures are common and intra-operative assays of parathyroid hormone can be used to confirm surgical success in minutes. Type II calcimimetic drugs that enhance the sensitivity of the calcium sensing receptor to calcium resulting in a decrease in PTH secretion are used in secondary hyperparathyroidism reducing the need for surgery in some patients[5], and may also have a selective role in complicated patients with PHPT and malignancy. In other areas surgery disappeared such as when initially H2 antagonists and later proton pump inhibitors (PPIs) replaced the need for gastric acid reduction by vagotomy.

However, some patients with metabolic problems have remained refractory to treatment despite the increased availability of medical management strategies in primary care which are adequate for the vast majority of cases. Two fields where the focus of secondary and tertiary care centres is increasingly on refractory disease are hypertension and hyperlipidaemia while in obesity and type 2 diabetes medical therapies are either inadequate or could be considered barely adequate to control disease progression in an increasing number

of patients. Recently there has been the start of a renaissance of surgical approaches to the management of these metabolic problems.

Obesity

Obesity is a fast increasing problem in the Western and developing worlds. As adiposity in the general population has increased the prevalence of morbid obesity $(BMI>40 \text{kg/m}^2)$ in the UK has risen from 1.5% (2000) to 2.4% (2009)[6, 7]. Lifestyle therapy is recommended for all patients and some patients with moderate obesity (BMI 27-35 kg/m²) receive additional weight-loss medications. However, the management of the morbidly obese has remained problematic. Many of these patients potentially qualify for bariatric surgery based on the NICE guidelines with qualifying criteria ranging depending on co-morbidities from BMI 35 to 50kg/m^2 and with BMI > 50kg/m^2 surgery is the preferred treatment option[8]. The most severe group in medical terms are those patients with established complications of obesity including diabetes and the sleep apnoea syndromes[9]. Classical diet approaches have proved inadequate in morbidly obese patients[10] who have invariably tried multiple diets. Orlistat, though often poorly tolerated, delivers a 3% average reduction in weight in moderately obese patients [11] and has evidence for a 37% reduction in progression to type 2 diabetes in compliant patients who achieved a net 4.8 kg weight loss[12]. Both sibutramine and rimonabant delivered more weight reduction when they were still available but were withdrawn due to side-effects [11]. Attempts are made to market novel compounds with a primary indication for diabetes on the basis of their weight loss properties but most are minimally more effective than metformin which delivers an average 2 kg (2%) weight reduction. The hyperbole associated with higher doses of liraglutide failed to note that it delivered an average glycaemic response for a hypo-glycaemic drug (1.0-1.2% HbA_{1c}) and only a 1.8-5.5 kg (2-5%) weight loss[13, 14].

Upper gastrointestinal surgeons have revived and modified many of their techniques to deal with obesity. Laparoscopic gastric banding, banded gastroplasty and gastric bypass are now frequently performed for weight reduction even in day surgery and have a developed a formidable evidence base. The Swedish Obesity Surgery registry has shown that complications rates are low (<2%), long-term mortality is acceptable for such a high-risk group (2%) and patients lose 20-40% of weight depending on the procedure [15, 16]. Series of laparoscopic surgery show acute deaths in only 0.23%[17]. Gastric bypass surgery is associated with reductions in glycaemia to the extent that 75% are restored to 'normoglycaemia' especially if the diabetes was of recent onset (<5 years), 50% of cases of hypertension and sleep appoea resolve and there is dramatic reduction in orthopaedic complaints allowing further surgery to occur if necessary[18]. After 7 years CHD mortality is reduced by 56%, diabetes mortality by 92% and cancer mortality by 60%. While the endocrinology of gastric bypass surgery has been partially clarified the mechanism by which gastric banding/gastroplasty works remains obscure. Though many anti-obesity drugs have been developed few have been either highly effective or safe[19]. Both implanted gastric stimulators to mimic the stretch reflex [20] and ghrelin agonists (e.g. MK-677 to reduce visceral adiposity)[21] and ghrelin binders in mice (Speigelmers)[22] have failed to duplicate the effect of surgery. In diabetes units the clinical problem is that many patients would benefit from operative intervention when assessed using health economic methods (BMI>30kg/m²) yet the capacity of the system to provide the bed space and finance is exceeded. Thus, many health systems ration access to bariatric surgery by limiting its availability to higher risk groups.

Hypertension

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Refractory hypertension is another common problem [23]. Some is caused by noncompliance with increasingly complex regimes, or due to the side-effects of non-specific vasodilation resulting in episodes of hypotension especially in patients with isolated systolic hypertension who have decreased vascular compliance. Many cases though are multi-factorial and associated with increasing age, obesity, renal dysfunction and left ventricular hypertrophy [23]. In the ALLHAT trial 27% of patients were not controlled despite triple therapy. This is not surprising as most anti-hypertensives deliver approximately a 10/5mmHg (6%) reduction. Many novel anti-hypertensives which seemed more effective in phase 3 studies have not reached clinical service. Angiotensin I-converting enzyme-neutral endopeptidase (ACE-I/NEP-I) inhibitors such as omapatrilat or samapatrilat delivered a 20/8mmHg (15%) reduction[24] but caused angioedema and were discontinued. The endothelin-I antagonist darusentan (LU-135252; HMR-4005) which remains in development reduced blood pressure by an added 18/11mmHg (11%) at a 300mg dose in patients with refractory hypertension in the DORADO study but was associated with high rates (30%) of peripheral oedema [25]. More recently, a combined angiotensin-II receptor neprilysin antagonist (LCZ-696) was shown to reduce blood pressure significantly (5/3mmHg) more than the angiotensin-II receptor blocker (ARB) valsartan [26]. Given the importance of the renin-angiotensin system in the prognosis of heart failure the 400mg dose is now being investigated in the PARADIGM-HF trial in 8940 patients[27].

Surgery, and recently percutaneous radiofrequency ablation[28, 29], is still used for the treatment of secondary hypertension caused by localised aldosterone or noradrenaline (norepinephrine) secreting tumours but it is increasingly recognised that most patients with aldosterone–driven hypertension actually show generalised adrenal cortical hypertrophy where surgery is inappropriate. Medical therapy with spironolactone, eplerenone or amiloride

is used for cortical hypertrophy. It has been known for many years from animal studies that neuronal adrenal/renal stimulation results in an increase in blood pressure. De-nervation surgery for hypertension was used prior to the invention of anti-hypertensive drugs[30]. In a series of 1266 patients which included 226 with end-organ damage and diastolic BP >140mmHg splanchnicectomy as opposed to sedation reduced 5-year mortality by 31% but sub-group blood pressure data was not provided[31]. Modern data was lacking until the recent SYMPLICITY-2 HTN study of 106 patients with refractory hypertension (systolic blood pressure >160mmHg; average 178/98mmHg) was conducted. In these patients most secondary causes had been excluded and they were on >3 anti-hypertensive drugs so meeting the definition of refractory hypertension. Percutaneous radiofrequency renal de-nervation resulted in a 32/12mmHg (20%) reduction in blood pressure at 6 months [32]. The hyperbole following this single small surgical trial will tempt many to attempt surgery for hypertension but given past history, it remains to be seen which patients will benefit most from this intervention[33]. It may only be a sub-group and if that is the case then clinical pathways have to be devised to optimally define the target group for future surgery. Similar concerns may also be relevant to a surgically implanted carotid bulb baroreceptor stimulator (Rheos) system which reduced blood pressure by 22/12mmHg in 45 patients with resistant grade 2 hypertension (179/105mmHg on 5 drugs) [34]. In this trial 17 patients achieved a 33/22mmHg reduction at 2 years and the device is now in phase 3 trials[35].

Hyperlipidaemia

Many think that hyperlipidaemia is treated solely by drug therapy. One common presentation to secondary care clinics is refractory hyperlipidaemia caused by side-effects to currently available therapies e.g. statins. Apheresis (dialysis/column extraction of lipoproteins) is effective in homozygous FH as patients are already secreting very low

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density lipoprotein (VLDL) at a maximal rate and many also show a limited response to statin therapy [36]. Apheresis has evidence from surrogate outcomes in homozygous FH. However, patients with heterozygous FH are poorer candidates for apheresis as their potential for increased rebound cholesterol synthesis is substantial. Though apheresis remains an option fo for the treatment of these individuals it relies on drug therapy to reduce the rate of rebound of LDL-C in the 2 week period between treatments so therapeutic options for drug-intolerant patients are very limited. Yet another option does exist and does have an evidence base.

Surgery was a potential option for treatment for hyperlipidaemia only 20 years ago. It is still used in homozygous familial hypercholesterolaemia (FH) where liver transplantation to restore hepatic LDL receptor function and particle clearance is common [37]. Some centres used to use **a** portocaval shunt to reduce triglyceride and cholesterol flux to the liver and resecretion of these in very low density lipoproteins (VLDL) and therefore eventually as low density lipoprotein (LDL)[38, 39].

Homozygous FH is an ultra-orphan disease (prevalence <1 in 10⁶) but surgery used to have indications in far less severely affected patients including those with heterozygous familial hypercholesterolaemia or severe polygenic disease. Ileal bypass surgery reduces LDL-C by a respectable 38%. The 834 patients in the Program on Surgical Correction of Hyperlipidemia (POSCH) study randomised to surgery or medical management showed a 35% reduction in coronary heart disease (CHD) events after 7 years [40]. In post-trial analyses this benefit continued and was associated with a 20% reduction in CHD mortality at 15 years [41] and further life benefit at 25 years[42]. These data are impressive as the surgery conducted at the time was open resulting in significant extra morbidity compared to modern minimally invasive techniques. An increase in events would be expected due to this and it is notable that in POSCH the time to survival curve divergence is 3 years. No studies have

examined the potential effectiveness of laparoscopic ileal bypass surgery in hypercholesterolaemia as opposed to diabetes and the metabolic syndrome [43, 44]. This procedure should deliver equivalent LDL-C reductions with a far lower inflammation burden and thus a quicker time to significant CHD event reduction. Randomised trials are difficult in this field but a prospective randomised open blinded endpoint (PROBE) design might be feasible.

The higher profile of orphan and ultra-orphan diseases has prompted the development of new therapies with narrow indications. High continuing costs are likely to be a feature of the novel lipid-lowering, hypertensive or obesity therapies being developed and especially those developed for orphan indications. It is likely that the microsomal transfer protein inhibitor lomitapide [45]; or the apolipoprotein B anti-sense oligonucleotide mipomersen[46] for severe hypercholesterolaemia will have high prices suited to their orphan indications for homozygous familial hypercholesterolemia in addition or as an alternative to apheresis rather than more general usage.

Type I and type V hyperlipidaemia are encountered in lipid clinics and are associated with pancreatitis and secondary diabetes. The primary therapies of fibrates, niacin, statins and omega-3 fatty acids are unsuccessful in patients with homozygous null mutations (often type I disease) of lipoprotein lipase (LPL) or its cell surface receptor GPIHBP1. They may be more useful in rescuing LPL deficiency secondary to deficiency of its activating co-factor apolipoprotein C2. However these drugs are most effective in type V hyperlipidaemia caused by the combination of heterozygous LPL deficiency allied with insulin resistance [47, 48]. Apart from supportive measures, bed rest and high dose anti-oxidants allied with acute plasmapheresis little can be done for type I hyperlipidaemia and therapeutic control can remain elusive. A few reports have suggested benefits of reducing chylomicron production by

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inhibiting fat absorption through prescription of the gastric lipase inhibitor orlistat[49]. Some case reports exist of occasional patients treated by bilio-pancreatic bypass surgery with claimed success [50, 51] in addition to the usual surgical management of the complications of recurrent pancreatitis. The potential alternative therapy for homozygous LPL deficiency is alipogene tiparvovec gene therapy for hypertriglyceridaemia which may be curative for LPL gene mutations and does reduce the incidence of pancreatitis but is likely to be extremely expensive [52].

Conclusion

It would be ironic if the next treatments for refractory hyperlipidaemia, hypertension or diabetes became surgical for reasons of superior cost economics as surgical procedures involve only a single intervention and lower follow-up costs as compared to high and continuing costs for pharmacological interventions (at least until expiry of any relevant patent)[53].

Declaration of Interest

ASW has received lecture honoraria from Aegerion Pharmaceuticals.

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