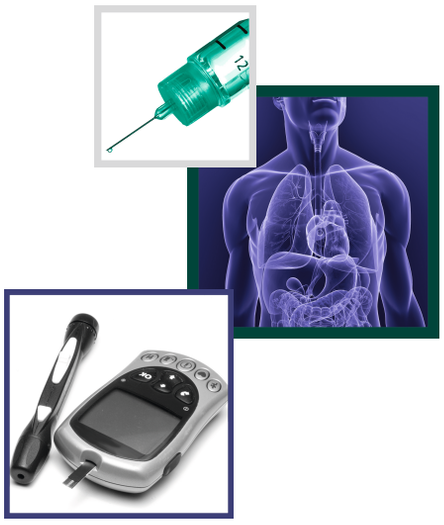
MANAGEMENT PERSPECTIVE

Childhood and adolescent obesity in cardiorenal metabolic syndrome and Type 2 diabetes: a clinical vignette and ultrastructure study



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Practice Points

- Assess to what the extent of a child or adolescent is overweight or obese in relation to other children at the same stage of development.
- Assess comorbidities associated with weight and treat these independently where appropriate.
- Assess end-organ involvement such as microalbuminuria, decreased glomerular filtration rate, impaired glucose tolerance, impaired fasting glucose, retinopathy, peripheral diabetic neuropathy and cardiovascular abnormalities such as hypertension or diastolic dysfunction.
- Assess why and how energy imbalance has occurred.
- Determine the level of clinical intervention required (sometimes referred to as staging).
- Prepare a treatment strategy with the patient and family.
- Outline treatment goals with outcome indicators not related to weight, such as exercise, physical endurance and/or generalized feeling of wellbeing.
- Review and provide regular assistance for weight management and maintenance of weight change and be prepared to revise the program if necessary.
- Remain involved in the care of your patients even if they are being seen by adolescent diabetic obesity programs.

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SUMMARY Childhood–adolescent overweight and obesity (CAOO) have grown to pandemic proportions during the past decade. The younger onset of obesity will have dire future complications manifesting as earlier onset end-organ disease in a disproportionate number of younger adults. This clinical snapshot begins with a clinical vignette of a 13 year old female with obesity, atherogenic lipid profile, hypertension with early urinary changes of chronic kidney disease and prediabetes. We have focused on the early ultrastructural changes found in two rodent models of obesity (Zucker obese [fa/fa] rat model of obesity, insulin resistance and prediabetes and db/db mouse model of obesity, insulin resistance and Type 2 diabetes mellitus) in their adolescent ages. Our focus is on remodeling in the obese adipose tissue, emphasizing the omental depot, the skeletal muscle, the islet and β cells and the end-organs including the myocardial and renal tissues. Obesity seems to be the driving force behind this process occurring in the skeletal muscle, islet and β cells, which constitutes the adipose–skeletal muscle–islet axis in the development of Type 2 diabetes mellitus. This current epidemic–pandemic of CAOO causes a red flag to be raised in order to have primary-care providers become more involved and understand this complex problem. The CAOO pandemic may alter the future course of human disease unless we as primary-care physicians intervene. For the first time the current generation may not live to be as old as their parents.

Clinical vignette

A 13 year old Caucasian female presents with a BMI of 30.2 (weight in kg; height in m^2) (80.96 kg [97 percentile-obese]; 1.8 m [74th percentile]), fasting elevated triglycerides (420 mg/dl), normal low density lipoprotein cholesterol (92 mg/dl) and decreased high density lipoprotein cholesterol (38 mg/dl). Liver function testing was normal. Fasting highly sensitive C-reactive protein measured 3.8 mg/l (normal–average risk up to 3 mg/l) without any clinical evidence for recent or current infection. Current laboratory did not provide ability to measure cytokine or adiponectin levels. Fasting thyroid stimulating hormone was in the normal range (2 mIU/l). Urinalysis was positive for microalbuminuria in two out of three morning-first voided specimens without glycosuria, estimated glomerular filtration rate (GFR) 88 ml/min/1.73 m^2, fasting blood glucose of 108 mg/dl with a 2 h postprandial glucose of 150 mg/dl (without polyuria or polydipsia). Blood pressure measurements on three separate occasions were reported as being in the prehypertension range, recently utilizing Wal-Mart blood pressure monitoring devices. Her current blood pressure is 140/88 mmHg in left arm and 144/86 mmHg in right arm after being seated for 5 min. The patient has not begun menarche at the time of examination. Physical examination is normal including secondary sexual development for chronological age and gender (Tanner Stage III–IV). The patient's mother is concerned because there is a positive family history of diabetes, cardiovascular disease and weight problems on both sides of the family.

Background

Childhood–adolescent overweight and obesity (CAOO) are major global public health concerns and this emerging pandemic is largely thought to be triggered by the same sociologic factors affecting adult overweight and obesity, consisting of increased sedentary lifestyles with physical inactivity and excess compact caloric consumption [1,2]. Childhood–adolescent overweight is defined as a BMI greater than the 85th percentile but less than the 95th percentile; whereas, Childhood–adolescent obesity is defined as those individuals having a BMI greater than the 95th percentile [3]. CAOO is associated with an increased prevalence (up to 50%) of the metabolic syndrome as presented in the clinical vignette and is increased on a graded scale based on increased half-units of increased BMI [4]. CAOO is also one of the most common causes of insulin resistance (IR) being associated with dyslipidemia, long-term cardiovascular complications including hypertension, prediabetes (impaired glucose tolerance [IGT]) and overt Type 2 diabetes mellitus (T2DM) [5,6]. Importantly, CAOO is associated with increased inflammation with an increase in the biomarkers C-reactive protein, IL-6, TNF-α and concurrent decreased levels of adiponectin (a marker of insulin sensitivity synthesized and secreted exclusively by adipocytes) [4,5].

Since we are unable to histologically sample the various tissues involved in CAOO patients, as presented in the clinical vignette, we have utilized two young adolescent rodent models of obesity, which may allow for a better understanding of the early remodeling changes in the involved tissues and end-organs [7]. Importantly, these ultrastructural observations in young rodent models strongly justify early intervention by the primary-care provider. These models consist of the 9 week old Zucker obese (ZO; fa/fa) rat model of IR, metabolic syndrome and prediabetes **(Figure 1)** and the 5 week old db/db obese – T2DM mouse model. Both models have mutations in

their leptin receptors resulting in hyperphagia – obesity and excessive redox stress – generation of reactive oxygen species (ROS) [7]. Because CAOO is associated with the emerging pandemic of IGT, prediabetes and overt T2DM, we will focus on the adipose–skeletal muscle–pancreatic islet β-cell axis and the early ultrastructural cellular and extracellular remodeling utilizing the transmission electron microscope (TEM). In addition, we will discuss the early ultrastructural remodeling found in the end organs of the kidney and heart representing the cardiorenal metabolic syndrome **(Figure 2)** [7–9].

Material & methods

A total of two well-known rodent animal models of obesity IR and T2DM were utilized for this investigation (db/db mouse and the ZO rat [fa/fa]).

Both rodent animal models have mutations in their leptin receptors resulting in hyperphagia, obesity, IR, T2DM and excessive generation of ROS.

■ db/db (C57BL/KSJ–db/db)

Young male db/db mice and their lean wild-type littermates (5 weeks of age) were obtained from Jackson laboratories (ME, USA).

■ ZO rat homozygous (fa/fa)$^{-(+/+)}$

Young male ZO and their heterozygous lean littermates (fa/$^{+}$) (9 weeks of age) were obtained from Charles River laboratories (MA, USA).

Immediately upon sacrifice, finely cut organ specimens were obtained and fixed in standard TEM fixative and prepared for viewing with a JOEL 1400-EX TEM. Ultrastructure – a fine structure, may be defined as the detailed structure of a biological specimen involving cells and the extracellular matrix of tissues or organs. All procedures were approved by the University of Missouri Animal Care Committees (MO, USA) and housed in accordance with NIH guidelines.

■ Important definitions

Remodeling implies a change of the cells and matrix in response to injury owing to

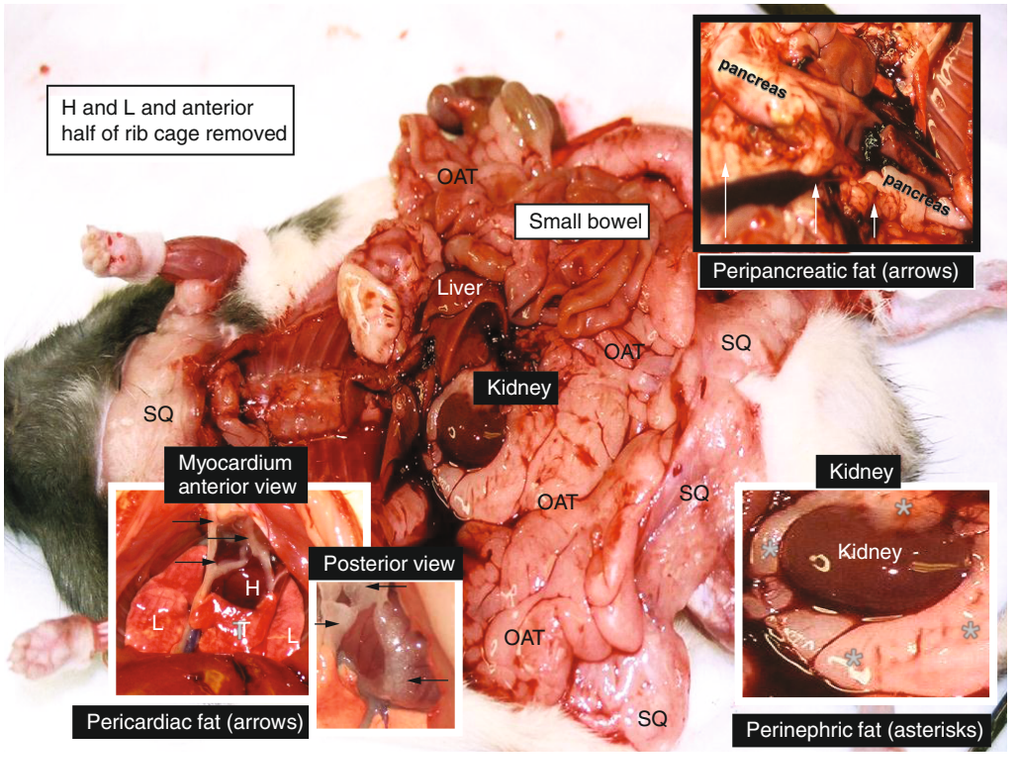

Figure 1. Gross findings of obesity in the 9 week old adolescent Zucker obese rat model.
Demonstrates the massive accumulation of OAT in the Zucker obese model. Also, note the excessive accumulation of SQ adipose tissue. Inserts depict the accumulation of peripancreatic fat (white arrows), pericardiac fat (arrows) and perinephric fat (asterisks).
H: Heart; L: Lung; OAT: Omental adipose tissue; SQ: Subcutaneous; T: Thymus.

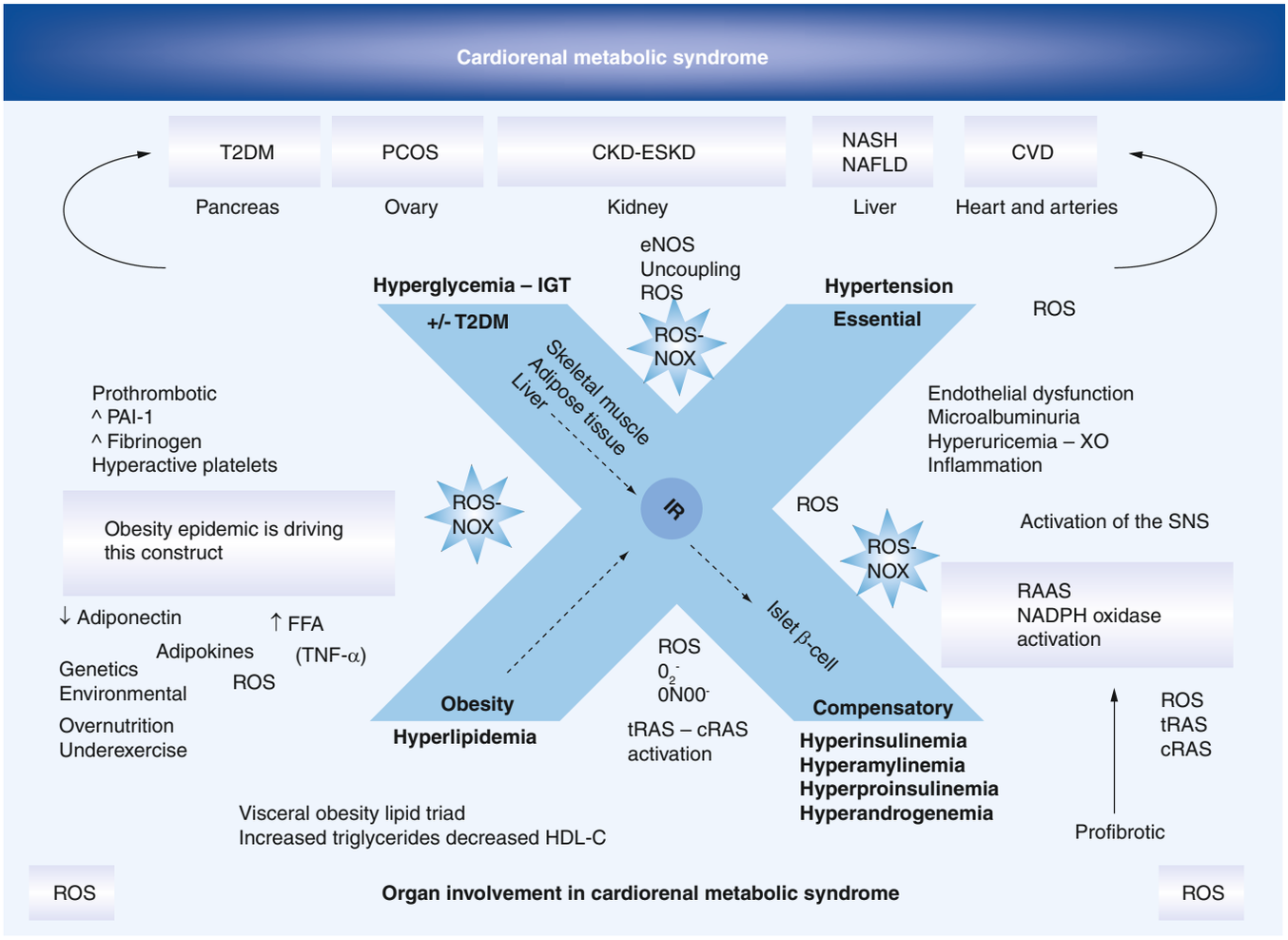

Figure 2. The cardiorenal metabolic syndrome. The cardiorenal metabolic syndrome has four arms, consisting of hyperlipidemia, hyperinsulinemia, hypertension and hyperglycemia (the four H's) represented by the letter X. This syndrome is driven by the obesity epidemic with its associated increases in FFAs, adipokines, ROS and decreased adiponectin secretion. Obesity (especially omental) drives skeletal muscle IR with associated hepatic and adipose IR (left lower arm of the X). In addition, IR results in a compensatory hyperinsulinemia, hyperamylinemia and hyperproinsulinemia, which activate both a local-tissue and cRAS, which also induces aldosterone secretion and SNS activation (right lower arm of the X). ROS elevation also induces endothelial dysfunction and these factors are individually and synergistically associated with hypertension (right upper arm of the X). Eventually, the islet pancreatic β-cells develop impaired insulin secretion and IGT with eventual β-cell failure – apoptosis with overt T2DM (left upper arm of the X). In time, each of the end organs (pancreas, ovary, kidney, liver, heart and arteries) are affected by adverse remodeling with increased morbidity and mortality.

CKD: Chronic kidney disease; cRAS: Circulatory renin–angiotensin system; CVD: Cardiovascular disease; eNOS: Endothelial nitric oxide synthase; ESKD: End-stage kidney disease; FFA: Free fatty acid; HDL-C: High density lipoprotein cholesterol; IGT: Impaired glucose tolerance; IR: Insulin resistance; NAFLD: Nonalcoholic fatty liver disease; NASH: Nonalcoholic steatohepatitis; NOX: NADPH oxidase; O2-: Superoxide; ONOO-: Peroxinitrite; PAI-1: Plasminogen activator inhibitor-1; PCOS: Polycystic ovary syndrome; RAAS: Renin–angiotensin–aldosterone system; ROS: Reactive oxygen species; T2DM: Type 2 diabetes mellitus; tRAS: Tissue renin–angiotensin system; XO: Xanthine oxidase.

Adapted with permission from [15].

physical or metabolic stress. The delicate balance between the process of oxidation–reduction and antioxidation are referred to as redox homeostasis. Redox stress occurs when there is a predominate imbalance and ROS causing injury to lipids, proteins and nucleic acids resulting in cellular and tissue injury with subsequent remodeling. ROS–redox stress (owing

to multiple metabolic toxicities) are elevated in CAOO patients and the rodent animal models presented.

Omental adipose tissue ultrastructural remodeling

The omental-visceral adipose tissue depot is thought to be the instigator of the metabolic syndrome and ultrastructural remodeling in skeletal muscle IR and subsequent compensatory pancreatic islet β-cell hyperinsulinemia with eventual fatigue and failure [7,10]. The adipose depots are not only the major storage sites for energy via retention of free fatty acids (FFA) and glycerol as triglycerides but also are important in their endocrine role secreting numerous peptide hormones. These hormones include adiponectin, leptin, resistin, inflammatory adipocytokines including TNF-α, IL-6 and various growth factors, which are capable of influencing distant end-organs such as skeletal and cardiac muscle, liver, pancreatic islet β-cells and the kidney [7–10].

The obese omental depot in the ZO rat model demonstrated the following ultrastructural remodeling: adipocyte hypertrophy, inflammatory changes with macrophage infiltration, which

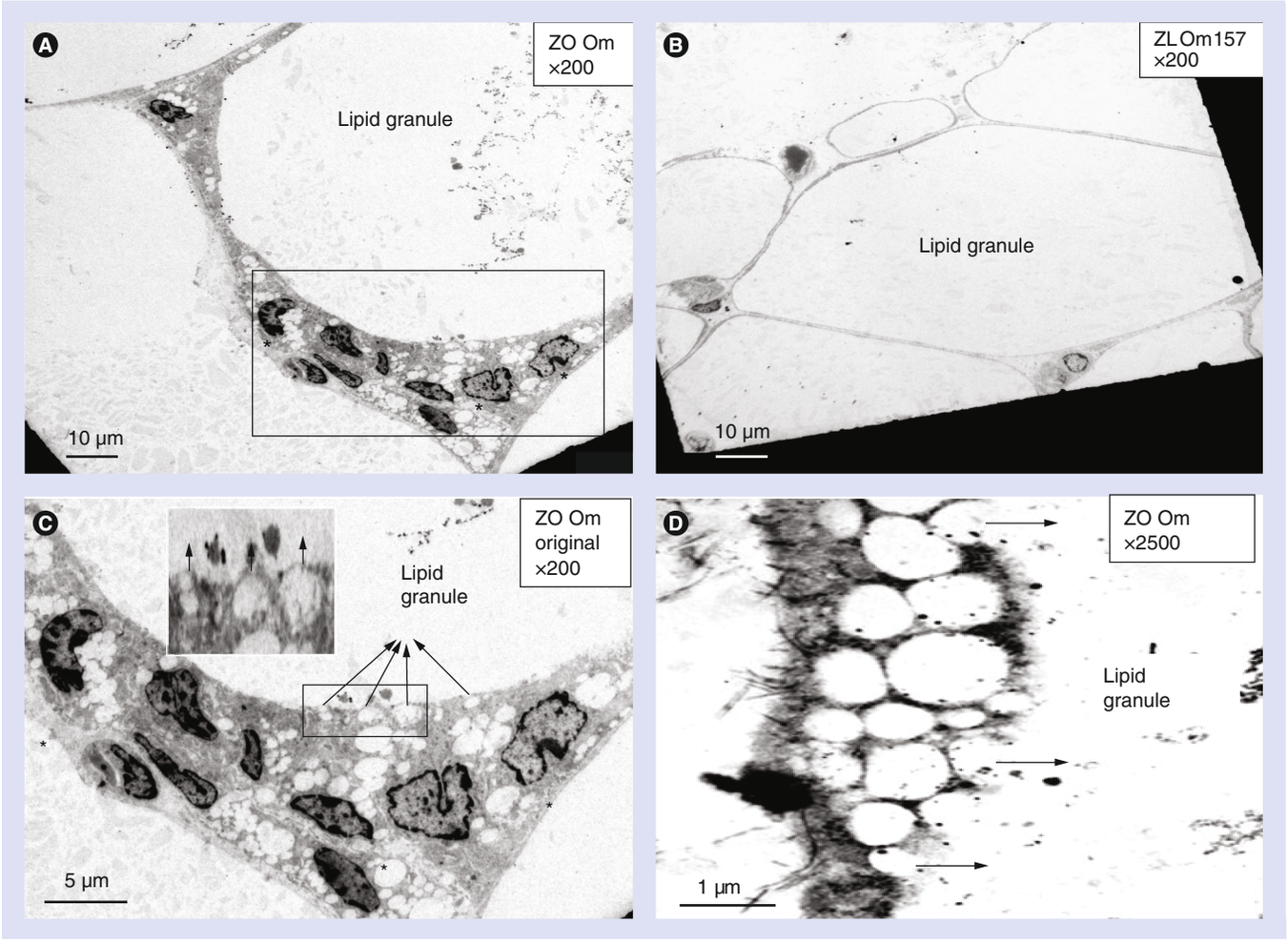

Figure 3. Ultrastructure remodeling of omental adipose tissue in the Zucker obese rat model. (A) Demonstrates adipocyte hypertrophy, interstitial widening and inflammatory infiltrate of macrophages (asterisks) in the ZO models as compared with the ZL control rat model in **(B)**. **(C)** Depicts the disgorging of smaller lipid vacuoles (arrows) of the macrophages into the large maturing unilocular lipid granule in addition to the cytoplasmic lipid vesicles–vacuoles disgorging into the lipid-laden adipocyte mature lipid granule (arrows) in **(D)**. These findings were only observed in omental ZO plasma membranes and inflammatory macrophages in the ZO omental adipose depots. Scale bars and magnification are clearly marked in **(A–D)**.
ZL: Zucker lean; ZO: Zucker obese.
Adapted with permission from [7].

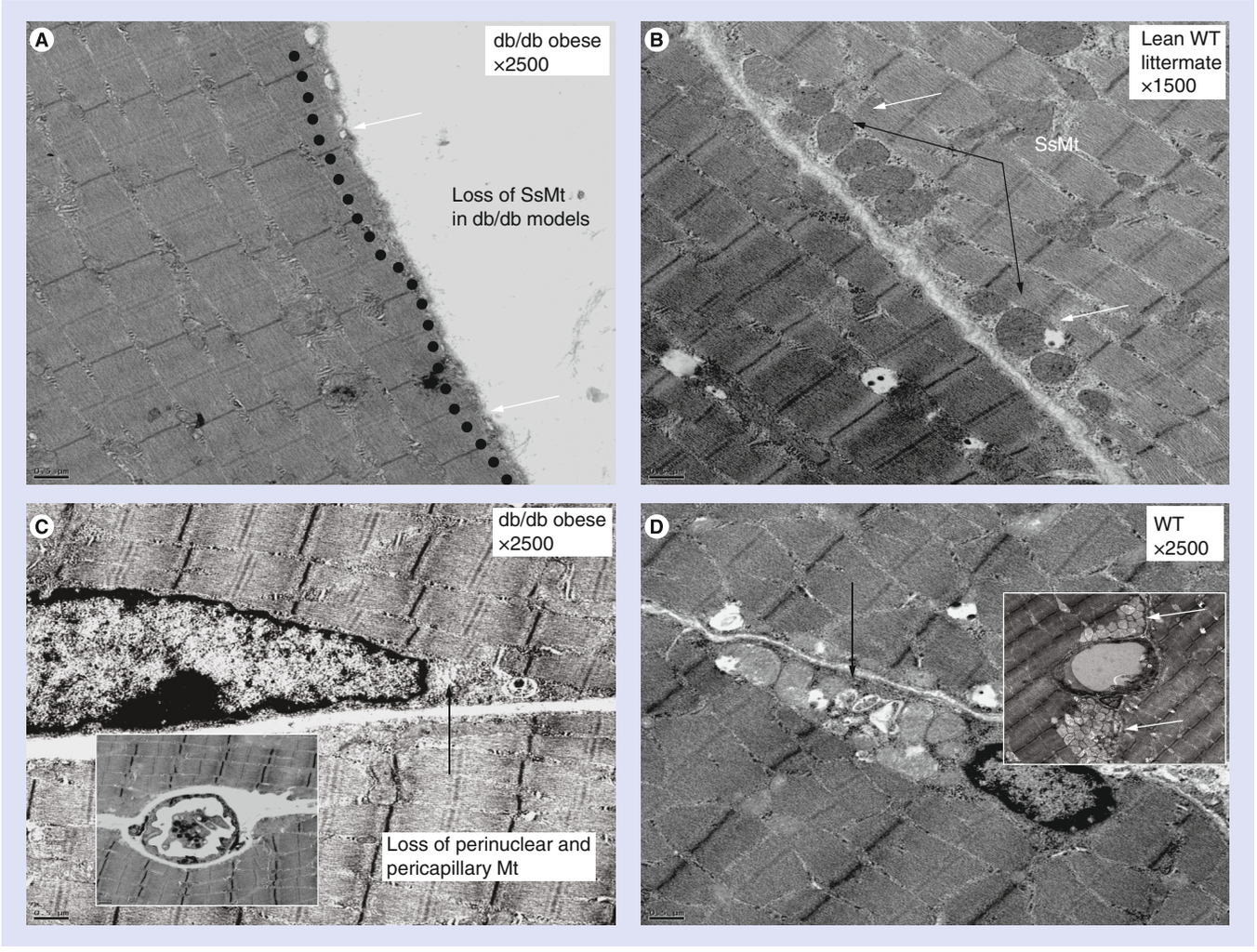

Figure 4. Obesity associated with loss of soleus subsarcolemmal, pericapillary and perinuclear mitochondria in the obese db/db mouse model. (A) Depicts the loss of SsMt (arrows – dotted line in db/db model as compared with the lean WT littermate **[B]**). **(C)** Demonstrates the loss of perinuclear pericapillary (inset) Mt as compared with lean WT (arrows) **(D)**. Scale bars = 0.5 μm **(A–D)**. Mt: Mitochondria; SsMt: Subsarcolemmal mitochondria; WT: Wild-type.

was not identified in the subcutaneous tissues of the ZO or any of the adipose depots in the Zucker lean rat littermates (not shown). In addition the adipocytes demonstrated disgorging of lipid vesicles–vacuoles into the lipid-laden adipocyte lipid granules (Figure 3). These ultrastructural observations in the young obese rat model may correlate to the possible findings of inflamed omental adiposity and obesity in the patient presented in the clinical vignette.

Skeletal muscle tissue ultrastructural remodeling

Elevated triglycerides and FFA derived from excessive lipolysis in the adipose depots with associated elevated TNF-α, ROS and decreased adiponectin are associated with increased adipose tissue depots. These metabolic abnormalities are known to interfere with insulin signaling in skeletal muscle and this occurs owing to an impairment in phosphorylation of the insulin receptor substrate-1 protein, which downregulates the glucose transporter-4 (*GLUT-4*) gene and impairs GLUT-4 translocation from the cytosol to the plasma membrane resulting in impaired glucose uptake in skeletal muscle. Importantly, this impaired glucose uptake IR and the compensatory hyperinsulinemia does not come without a price, namely IR and increased oxidative stress as a significant part of the multiple metabolic toxicities [7,8,11].

Skeletal muscle ultrastructural remodeling demonstrates a loss of subsarcolemma, perinuclear and pericapillary mitochondria in the soleus (slow twitch) muscles **(Figure 4)**. Interestingly, there are current scientific reasons for the possibility that IR and the compensatory hyperinsulinemia may also contribute to development of obesity owing to the development of adipose depot IR and the direct metabolic effects of IR and hyperinsulinemia on adipocytes [11]. The observational findings in the db/db obese animal model presented have been shown to be present in human subjects [12] and therefore, may be representative of possible biopsy findings in our patient presenting with IGT in the clinical vignette.

Hepatic IR

It is not within the scope of this clinical snapshot to go into great detail regarding hepatic IR and remodeling, since our focus is on the adipose–skeletal muscle–islet axis. However, insulin is known to have suppressive effects on glucose production by its direct effects on hepatocytes and indirect effects involving suppression of adipose tissue lipolysis with reductions in FFA.

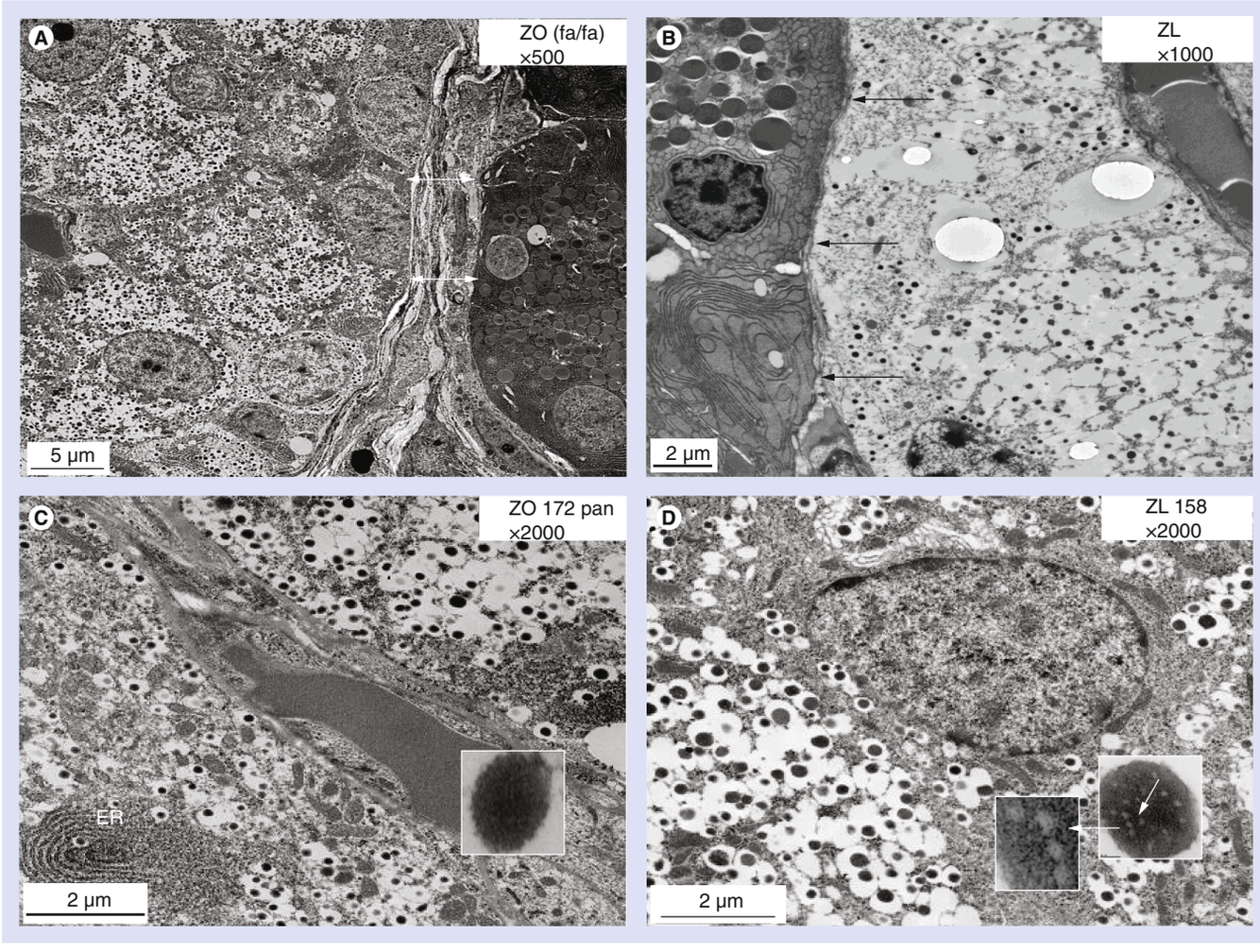

Figure 5. Widening of the islet exocrine interface and depletion of insulin secretory granules in the Zucker obese rat model.
(A) Illustrates a marked widening of the islet exocrine interface (double arrows) in the ZO rat model with only half the magnification as compared with the ZL model **(B)** (single arrows). Bar = 5 µm. **(C)** Demonstrates decreased insulin secretory granule (electron-dense black dots) and increased ER as compared with the ZL rat in **(D)**. Bar = 2 µm. Note the loss of 7–10 nm electron lucent Hayden–Sowers bodies (arrows **[D]**) in exploded insert image of an ISG of the ZO rat model in **(C)**.
ER: Endoplasmic reticulum; ZO: Zucker obese; ZL: Zucker lean.
Adapted with permission from [7].

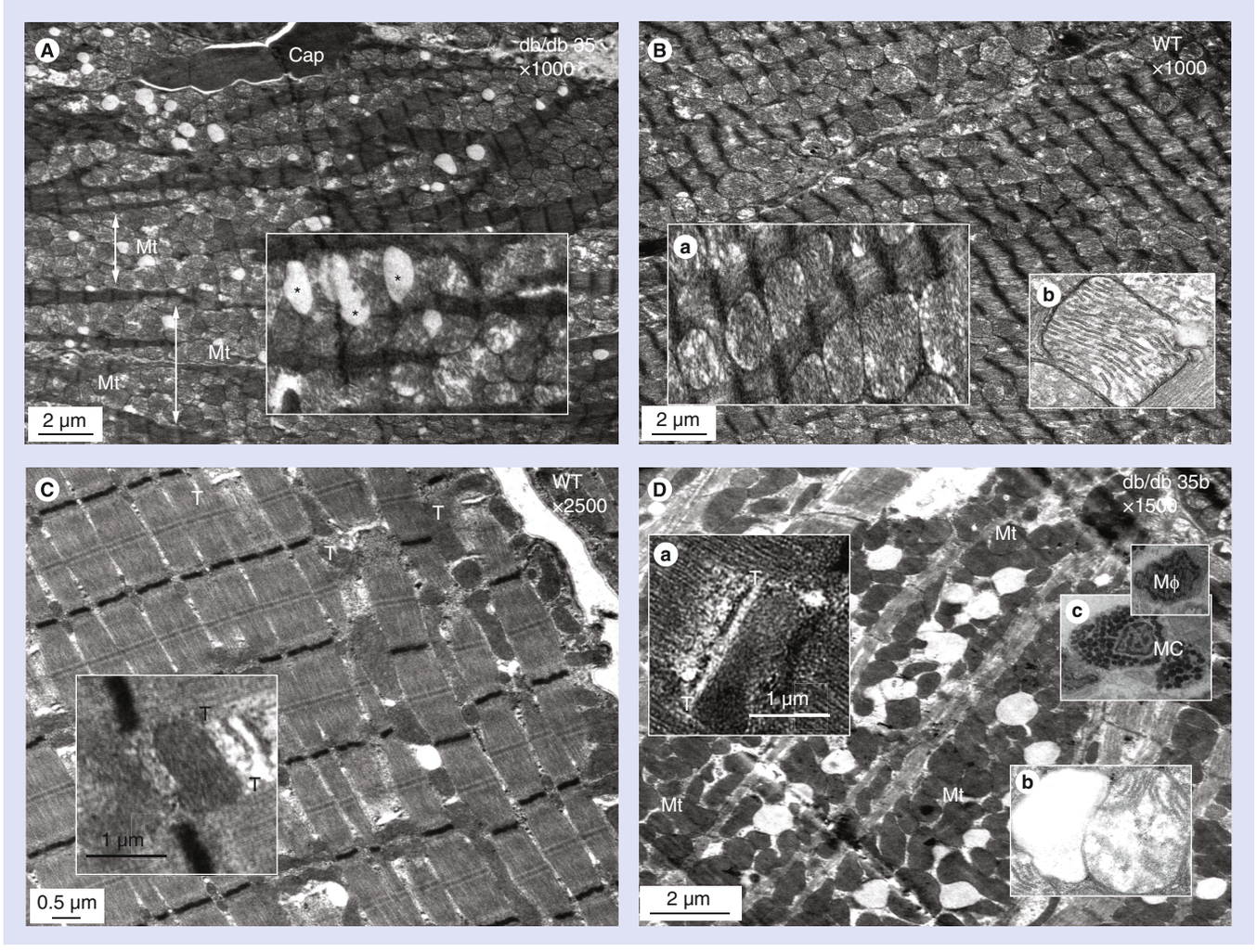

Figure 6. Myocardial intermyofibrillar lipid and abnormal mitochondrial deposition in the db/db mouse models of obesity and Type 2 diabetes mellitus with compression of T-tubules, sarcoplasmic reticulum and early chronic inflammation. (A) Depicts marked deposition of electron lucent lipid granules (asterisks) and Mt in the intermyofibrillar regions of myocardium in the db/db models as compared with the WT lean littermates in **(B)** and **(C)**. **(D)** Depicts the compression of the sarcoplasmic reticulum and T (insert a). These Mt, while increased in number, have lost their cristae and matrix (insert b) as compared with **(B)** (insert b). Note the compression of the T in **(D)** (insert a) as compared with insert in (**C**). Furthermore note the presence of both Mϕ and MCs representing chronic inflammation in (**D**) (insert c) of the db/db models, which was not present in any of the WT models.
Mϕ: Macrophages; MC: Mast cell; Mt: Mitochondria; T: T tubules; WT: Wild-type.

Thus, IR hyperinsulinemia results in increased gluconeogenesis and increased lipolysis resulting in increased glucose and FFA. IR of hepatic tissue plays an important role early in the development of the cardiorenal metabolic syndrome and T2DM. Similar to the other organ tissues discussed, the liver may also be abnormally affected by obesity owing to the multiple metabolic toxicities with the development of nonalcoholic fatty liver disease (NAFLD) or nonalcoholic steatohepatitis (NASH). Interestingly, hepatic IR can occur in the absence of NAFLD or NASH. NAFLD represents a spectrum of fatty liver disorders with evolving remodeling changes ranging from hepatic steatosis to NASH, fibrosis, cryptogenic cirrhosis and end-stage liver disease. A detailed discussion of this clinical snapshot by Ortiz-Lopez C *et al.* is recommended [13].

Hepatic IR and systemic IR – hyperinsulinemia associated with increased gluconeogenesis and increased lipolysis resulting in increased glucose and FFA.

IR results in compensatory pancreatic ultrastructural islet remodeling

Pancreatic islet ultrastructural remodeling in the ZO rat consists of widening of the islet exocrine interface – peri-islet regions, insulin secretory granule (ISG) loss – depletion and loss of electron lucent Hayden–Sowers bodies (Figure 5). This remodeling is felt to indicate maturity of insulin and amylin synthesis in ISGs. In addition, islet hypertrophy, increased golgi and endoplasmic reticulum (ER) in β-cells indicating ER stress, periductal islet (β-cell) neogenesis, peri-islet pericyte hyperplasia and angiogenesis were also detected. Compensatory hyperinsulinemia and hyperamylinemia develop in obesity owing to skeletal muscle IR and the compensatory pancreatic response. Importantly, these hormones contribute to the local and systemic activation of the renin–angiotensin–aldosterone system and SNS and consequent development of the cardiorenal metabolic syndrome [7,8]. It is

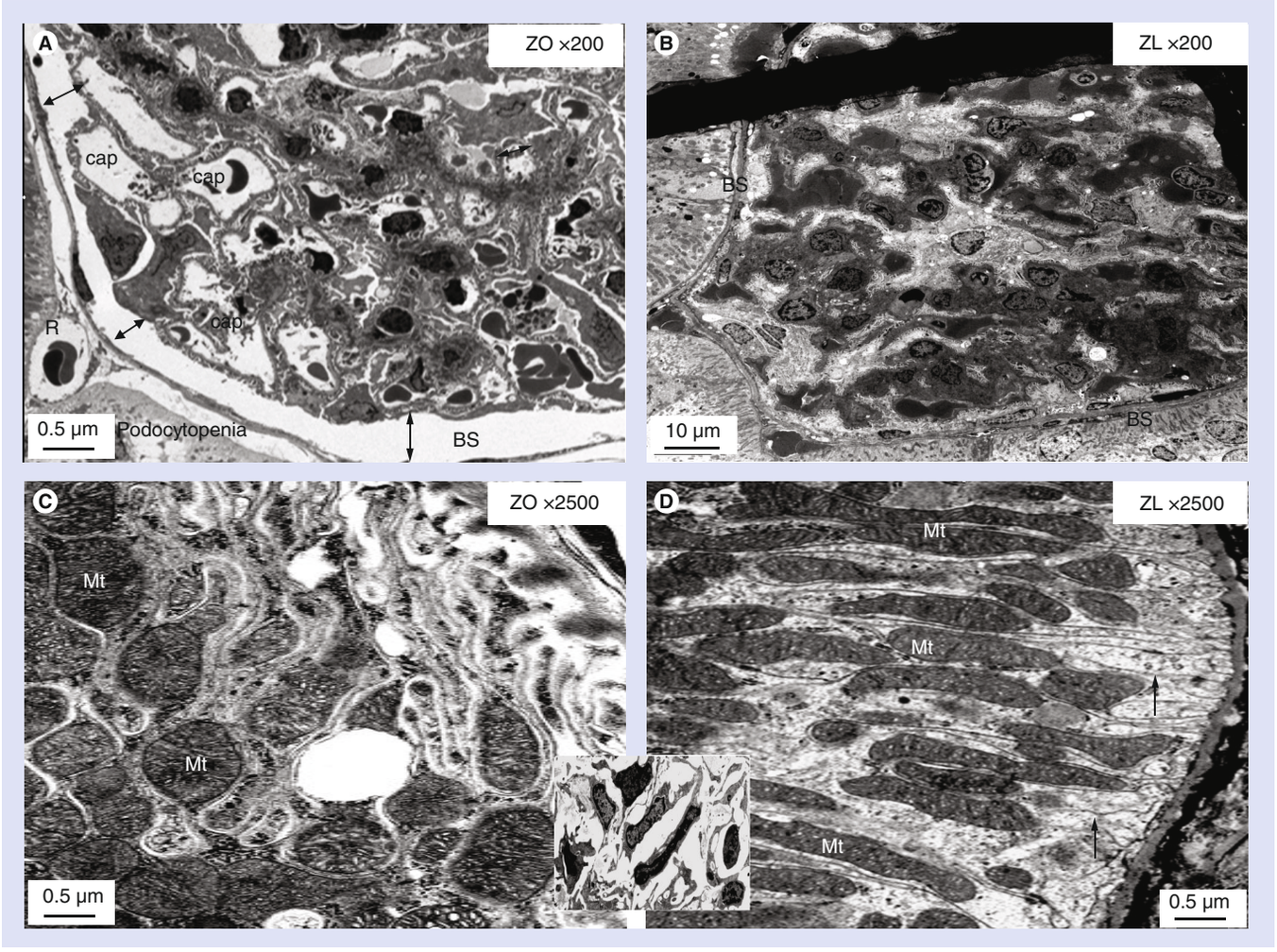

Figure 7. Obesity-related glomerulopathy tubulopathy in the young Zucker obese fa/fa rat model. (A) Depicts glomerular hypertrophy, widened BS, dilated glomerular capillaries, podocytopenia, with reduced podocyte/endothelial cell ratio (not shown) and R formation as compared with the ZL rat littermate in **(B)**. **(C)** Depicts a loss of basolateral polarity, chaotic disorganization of the basolateral regions of the proximal tubule with loss of Mt elongation termed Mt fragmentation and loss of the canalicular infoldings. These changes may represent the earliest changes of epithelial mesenchymal transition or early loss of proximal tubule cells in the ZO model. Insert between **(C)** and **(D)** depicts interstitial chronic inflammation with monocytes and macrophages in the interstitium predisposing to fibrosis.
BS: Bowman's space; Mt: Mitochondria; R: Rouleaux; ZL: Zucker lean; ZO: Zucker obese.
Adapted with permission from [7].

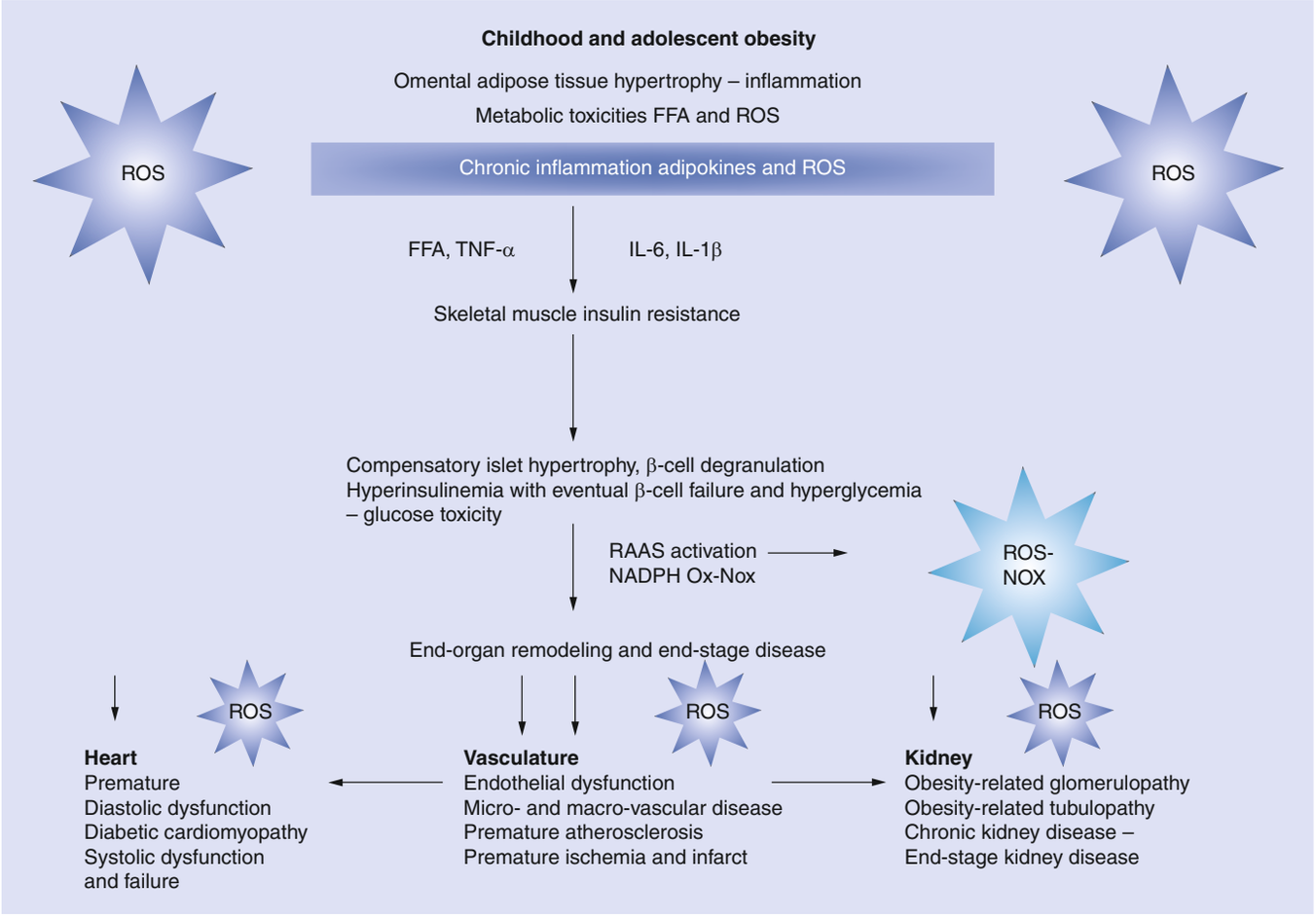

Figure 8. Childhood adolescent overweight and obesity flow chart. From childhood adolescent obesity to chronic inflammation, adipokines and ROS to excess FFAs and adipokines (TNF-β, IL-6 and IL-1β) to skeletal muscle insulin resistance and impaired glucose uptake to compensatory islet hypertrophy and hyperinsulinemia with insulin secretory granule depletion-degranulation and eventually failure to RAAS and ROS generating activation of the NOX to end-organ remodeling and end-stage disease.
FFA: Free fatty acid; NOX: NADPH oxidase; RAAS: Renin–angiotensin–aldosterone system; ROS: Reactive oxygen species.

not feasible to obtain pancreatic biopsies in our CAOO patients. Therefore, the images presented in a comparable adolescent obese model (Figure 5) indicate the depletion of ISGs and increased ER, which correlates to IGT with increased fasting and 2 h postprandial blood glucose in the patient described in the clinical vignette.

End-organ ultrastructural remodeling

■ Heart myocardium

In addition to the myocardium the macro- and microvascular system are involved. The myocardium demonstrates considerable end-organ ultrastructural remodeling in the db/db mouse model of obesity and T2DM similar to the ZO rat model. The db/db mouse models demonstrated a marked increase in intermyofibrillar lipid and abnormal appearing mitochondria deposition suggesting mitochondrial biogenesis displacing normal cardiomyocyte structure (Figure 6). Importantly, the T-tubules and sarcoplasmic reticulum are compressed and may result in dysfunction with abnormal calcium handling contributing to the diastolic dysfunction present in these animal models and also in humans. The T-tubules also contain glucose transporter protein receptors in addition to the sarcolemma [14] and the observed compression may also contribute to impaired glucose uptake and myocardial IR. The remodeling changes in the ZO rat model of the myocardium has been previously described and consists of diastolic dysfunction typical of diabetic cardiomyopathy and decreased insulin

sensitivity, increased intermyofibrillar mitochondria (biogenesis) and disordered myocyte ultrastructure, pericapillary fibrosis and interstitial fibrosis, abnormal swollen mitochondria with decreased cristae and matrix electron density and collapsed capillaries [15]. These early ultrastructural remodeling changes in the obese adolescent Zucker rat model of obesity may help to understand the predisposition to the premature development of diastolic dysfunction that may have already developed in the patient presented in the clinical vignette.

■ Kidney, chronic kidney disease & end-stage kidney disease

The young 9 week old ZO rat model of IR and obesity is known to develop microproteinuria (microalbuminuria) and therefore, may serve as an excellent model of CAOO abnormalities in CAOO human patients [16]. The kidney undergoes marked ultrastructural remodeling in this 9 week old rat model consisting of: glomerular hypertrophy and widening of Bowman's space, inflammation, loss of podocytes, podocyte remodeling; these changes have been described in humans and are termed obesity-related glomerulopathy. In addition, there is marked ultrastructural remodeling of the proximal tubule, which is similar to another rodent model of IR and excess angiotensin II production (owing to renin transfection with the mouse renin gene) in the Ren2 model of hypertension and IR [17]. In the young ZO rat model we now refer to these proximal tubule cell remodeling changes as obesity-related tubulopathy **(Figure 7)**. The patient in the clinical vignette presented with microalbuminuria and a decreased GFR and was not biopsied; however, similar remodeling changes may be present if the kidney were biopsied similar to those patients with obesity-related glomerulopathy.

■ Pancreatic islet & T2DM

In addition to the early islet compensatory remodeling associated with skeletal muscle and systemic IR, the pancreatic islets may also undergo targeted end-organ remodeling consisting of advanced islet exocrine interface fibrosis, increasing β-cell dysfunction and apoptosis, islet amyloid deposition and β-cell failure with a progressively diminished capability of insulin's availability [18]. This progressive islet remodeling may eventually result in the need for daily exogenous insulin therapy.

Some possible interventions in the clinical vignette: how we may approach this epidemic

The 13 year old female is adolescent and obese with an atherogenic lipid profile. She is presenting with microalbuminuria and decreased GFR with impaired fasting blood glucose and IGT translating to the prediabetic state. She has hypertension and a normal physical examination.

■ Possible approaches

The primary-care provider is already at an advantage in that the mother accompanies the patient and this signals that at least one of the two parents is immediately 'on-board' to become involved with this patient's recommendations and therapies. First, diet is extremely important with discussion regarding fast-food intake and portion size. Appropriately, the patient should be referred to a nutrition dietician for expert counseling who is familiar in dealing with the CAOO epidemic and their eating habits. This patient should be monitored very carefully for adherence because she already demonstrates that the cardiovascular system (hypertension), islet function (impaired fasting glucose and IGT with prediabetes) and renal (microalbuminuria and decreased GFR) involvement. All soft drinks should be immediately discontinued and replaced with water or diet-free soft drinks and encouraged not to discontinue milk; however, skimmed milk should be utilized in order to continue a proper calcium balance for growth. Portion size should be limited and a diet rich in fruit and vegetables encouraged. Exercise cannot be emphasized enough in these patients as even walking exercise improves skeletal muscle IR even prior to weight reduction.

There is time to initiate lifestyle changes and not institute pharmacotherapy but the primary-care provider should not wait for more that 3 months owing to the early end-organ involvement.

The most commonly used medication in these CAOO patients is metformin because it is an antidiabetic drug that is known to improve insulin sensitivity as well as being the only US FDA approved oral treatment for youths with T2DM [19]. The patient herself volunteered this question: 'Could my medical problems explain why my periods have not come yet?' The answer is definitely yes because she may have developed polycystic ovary disease associated with her underlying metabolic abnormalities. This patient's blood pressure elevation and reduced GFR are the most threatening and deserve close monitoring. If there

is no response to lifestyle changes within a month then medication such as metformin should be strongly considered. The overall goal should be to work with this patient closely until all metabolic parameters have returned to the normal range. In addition, she is a patient who would be a good candidate for referral to an adolescent diabetic obesity program, which are present at many teaching hospitals across the nation. Encouragement should be given to the patient and family for follow-up visits to the doctor, the primary-care provider, to work with the referral center in order to coordinate the recommended treatment plan closer to home in a more familiar setting and surrounding.

There is a great deal of information regarding the various approaches that the primary-care provider can obtain in addition to the practice points outlined previously [20–23].

Conclusion

The CAOO epidemic appears to be the driving force behind the development of cardiorenal metabolic syndrome, IR, T2DM, cardiovascular disease, CKD and increased oxidative-redox stress and ROS in young rodent models as well as human CAOO patients **(Figure 8)**. Importantly, the two rodent animal models may serve as excellent examples of the quite similar epidemic in humans. The combination of IR and ROS are strongly implicated at each turn of the cardiorenal metabolic syndrome, prediabetes, and overt T2DM. Abnormal environmental lifestyles (inadequate exercise and excess compact calories), genetics and epigenetics resulting in obesity play such a crucial role from the instigation to the complicated end-organ remodeling resulting in multiple diabetic opathies.

The association of T2DM and obesity has been known for decades and the strong link between the two resides in the ability of obesity to engender IR initially in the skeletal muscle and later to involve the systemic end-organs affected by IR including the liver, adipose depots, heart, kidney and the islet cells of the pancreas. The compensatory increase of the β cells to overcome this IR is responsible for β cell ER stress, insulin metabolic signaling defects with secretory impairments – β-cell fatigue and eventually failure largely owing to apoptosis, which allows the primary care physician to better understand the 'adipo–skeletal–islet IR axis' in the development of T2DM in CAOO. In the past decade we have witnessed an explosion of these abnormalities with the CAOO epidemic concurrent with the pandemic of T2DM. In this brief overview we have attempted to demonstrate the earliest ultrastructural remodeling changes in obese adolescent rodent animal models, which may allow primary-care providers the first opportunity to see the critical cellular remodeling that is occurring in the organs responsible for this pandemic as well as the affected end organs. The complex orchestration of metabolic signaling involving several proteins along with the detrimental role of ROS (function) as well as the marked ultrastructural cellular and tissue remodeling (structure) interact to result in the initial development of abnormalities, which contribute to the initial development and the eventual end-organ complications.

While these representative remodeling changes have been demonstrated in adolescent rodent models, we hypothesize that these changes may be concurrently occurring in our CAOO patients. The early cellular/extracellular remodeling changes will definitely give rise to the earlier clinical presentations of not only the presenting diseases of overweight and obesity but also give rise to the involved end-organs such as the adipose depots, skeletal muscles, pancreatic islets, myocardium and kidney. These shared ultrastructural images allow us to better understand why these CAOO patients may be at a much greater risk for developing the clinical presentations and the morbid clinical complications of earlier onset major end-organ diseases. These associated diabetic opathies include atherosclerosis, accelerated atherosclerosis and intimopathy, diabetic cardiomyopathy, isletopathy, retinopathy, neuropathy, chronic kidney disease and diabetic nephropathy with their associated increased morbidity and mortality. At his early stage of compensatory remodeling and end-stage remodeling it may be possible to prevent or delay the ongoing remodeling in our patients. However, once fibrosis, or islet amyloid deposition occur these changes may result in a permanent impairment of organ–tissue function.

The images presented in this brief clinical snapshot only provide a snapshot in time; however, they do provide emerging evidence suggesting that obesity in young adolescent rodent models lead to increased abnormal ultrastructural remodeling. These cellular and extracellular remodeling changes are related to the overt microproteinuria, diastolic dysfunction, and the hyperglycemia of prediabetes observed in models thus far explored. Future directions should test the hypothesis as to whether renin–angiotensin–aldosterone system blockade and unique antioxidant β-blockers

known to increase the bioavailability of nitric oxide (nebivolol) may reduce this microproteinuria along with improved glomerular and proximal tubular ultrastructure remodeling.

The current treatments for CAOO center on life-style interventions including the proper diet and adequate exercise for our CAOO patients. Currently, the intervention utilizing pharmacotherapy consists of metformin for these individuals who do not respond to lifestyle interventions. Already some children with CAOO and T2DM may require insulin and other medications proven to be safe and effective. In the future we need to explore newer pharmacologic treatment modalities and bariatric surgical interventions. These future interventions will require testing of their safety and efficacy outcomes. To obtain an overview of these medications known to provide the proper pharmacotherapy the reader is directed to recent papers [19,23].

The continued increase in the prevalence of CAOO may alter the future course of human disease unless primary-care physicians acutely intervene and this is why we need to better understand this disease and the early cellular and tissue remodeling changes.

Future perspective

It will be interesting to see if this epidemic-pandemic can be slowed or reversed. The initiative of the primary-care provider, parents and the newly formed adolescent diabetes obesity programs will be crucial in order for this change to occur. A healthcare team approach will be an essential component to accomplish the goals of slowing or reversing this current epidemic–pandemic of CAOO. Some states have already developed programs that have been successful such as the state of Minnesota and the following website provides more detailed information for those interested: [101].

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Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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