



Gnudi, L., Coward, R. J. M., & Long, D. A. (2016). Diabetic Nephropathy: Perspective on Novel Molecular Mechanisms. *Trends in Endocrinology and Metabolism*, 27(11), 820-830.
<https://doi.org/10.1016/j.tem.2016.07.002>

Peer reviewed version

License (if available):
CC BY-NC-ND

Link to published version (if available):
[10.1016/j.tem.2016.07.002](https://doi.org/10.1016/j.tem.2016.07.002)

[Link to publication record in Explore Bristol Research](#)
PDF-document

This is the accepted author manuscript (AAM). The final published version (version of record) is available online via Elsevier at <http://dx.doi.org/10.1016/j.tem.2016.07.002>. Please refer to any applicable terms of use of the publisher.

University of Bristol - Explore Bristol Research

General rights

This document is made available in accordance with publisher policies. Please cite only the published version using the reference above. Full terms of use are available:
<http://www.bristol.ac.uk/red/research-policy/pure/user-guides/ebr-terms/>

1 **Diabetic nephropathy: perspective on novel molecular mechanisms**

2
3 Luigi Gnudi,¹ Richard JM Coward,² David A Long.³

4
5 ¹Cardiovascular Division, King's College London, SE1 9NH, UK;

6 ²Academic Renal Unit, Dorothy Hodgkin Building, University of Bristol, Whitson Street,
7 Bristol BS1 3NY, UK;

8 ³Developmental Biology and Cancer Programme, Institute of Child Health, University
9 College London, WC1N 1EH, UK.

10
11 **Corresponding Authors:**

12 Luigi Gnudi, e-mail : luigi.gnudi@kcl.ac.uk

13 David Long, PhD, e-mail : d.long@ucl.ac.uk

14
15
16
17
18 Word count: 3617

19
20
21
22
23
24
25 Keywords: diabetes, glomerulus, oxidative stress, podocytes, endothelium, SGLT2

27 **Abstract**

28 Diabetes is the major cause of end stage renal disease globally, and novel treatments
29 are urgently needed. Current therapeutic approaches for diabetic nephropathy are
30 focusing on the inhibition of the renin angiotensin aldosterone system, on glycaemic
31 and lipid control, and life style changes. In this review we will highlight new molecular
32 insights in our understanding of the initiation and progression of diabetic nephropathy
33 including glomerular insulin resistance, dysregulation of cellular substrate utilisation,
34 podocyte-endothelial communication and inhibition of tubular sodium coupled glucose
35 reabsorption. We believe these mechanisms offer new therapeutic targets that can be
36 exploited to develop important renoprotective treatments for diabetic nephropathy over
37 the next decade.

38

39 **INTRODUCTION**

40 Diabetes mellitus is a metabolic disorder associated with chronic micro- and
41 macrovascular complications. One of the most feared chronic microvascular
42 complications is diabetic nephropathy (DN), currently the leading cause of end-stage
43 renal disease (ESRD) in the Western world. Strikingly, 40-45% of patients with type-1
44 diabetes (T1D) develop DN and reach ESRD or die before its onset. Moreover,
45 clinicians face a ~30% prevalence of patients with type-2 diabetes (T2D) and DN, with
46 45% of patients currently on dialysis having a primary diagnosis of diabetes, a
47 population also at high risk of developing cardiovascular disease [1].

48

49 An early sign of DN is an increased amount of urinary protein, manifested by
50 “albuminuria”, which correlates with, and can predict, the progression of renal damage.
51 Albuminuria arises from defects in the permeability of the glomerular filtration barrier
52 consisting of glomerular endothelial cells (GECs) separated from specialized epithelia,
53 called podocytes, by the glomerular basement membrane (GBM)[1]. Podocytes have
54 extensive inter-digitating foot processes connected together by a slit diaphragm
55 composed of proteins including nephrin and neph1, which interact with cytoplasmic
56 adaptor and signalling proteins (PI3-Kinase, CD2AP, AKT, podocin). Nephrin is also
57 linked with the podocyte actin cytoskeleton; the protein tyrosine kinase Fyn promotes
58 nephrin phosphorylation which enhances its interaction with PI3-Kinase and PI3K-
59 dependent phosphorylation of AKT and subsequently increases Rac1 activity, leading
60 to modification of the actin cytoskeleton with maintenance of a normal podocyte
61 anatomical structure and function [2, 3]. The structure and integrity of the glomerulus
62 is also maintained by a complex local autocrine/paracrine network between the
63 podocyte and the GECs consisting of vascular growth factors and vasoactive peptides

64 which is disrupted in DN [4]. The GECs are highly fenestrated with a unique
65 ultrastructure lacking fenestrae diaphragms which facilitate water and small solutes
66 permeability [5]. GECs are covered by a glycocalyx consisting mainly of proteoglycans
67 which include core proteins such as syndecan and attached glycosaminoglycan side
68 chains which appear to be important in regulating the permeability of the glomerulus
69 [6].

70

71 Animal and human studies have established that the metabolic and haemodynamic
72 changes that occur in diabetes lead to ultrastructural alterations of the glomerular
73 filtration barrier, including podocyte foot process fusion and detachment, GBM
74 thickening, a reduced endothelial cell glycocalyx, mesangial extracellular matrix
75 accumulation and glomerulosclerosis (**Figure 1**). These structural glomerular changes
76 correlate with increasing albuminuria which has been proposed to be a marker of
77 generalised systemic vascular dysfunction by the “Steno hypothesis” [7] and could
78 represent a common pathogenetic mechanism for renal and extra-renal chronic
79 vascular complications in diabetes [1].

80

81 Over the last 5-10 years our understanding of the molecular and cellular pathways by
82 which diabetic kidney disease results in damage to the glomerular filtration barrier has
83 increased. In this review, we will outline recent advances in glomerular insulin
84 signalling, oxidative and endoplasmic reticulum (ER) stress and podocyte-endothelial
85 communication that have revealed new exciting therapeutic directions for DN.

86

87

88 **Insulin resistance as a mechanism for the predisposition of DN**

89 Insulin is a metabolic hormone which not only regulates glucose and the metabolism
90 of other substrates but also directly modulates the biology of specific cells in a variety
91 of tissues. In both T1D and T2D patients, the ability of insulin to elicit cellular responses
92 is impaired, a concept termed “cellular insulin resistance”, and is associated with DN
93 [8]. Insulin resistance correlates with the development of microalbuminuria both in T1D
94 and T2D patients and patients with T1D with DN are more likely to have a strong family
95 history of insulin resistance when compared with those without DN [9]. Insulin
96 resistance has been implicated in the development of glomerular hypertension and
97 hyperfiltration [10], seen in the initial phase of diabetic kidney disease [11].
98 Furthermore, in both T1D and T2D patients, insulin resistance *per se* contributes to
99 higher salt sensitivity, which closely associates with increases in blood pressure,
100 albuminuria, and a decline in renal function [12, 13].

101

102 Within the kidney many different cell types are insulin sensitive and express functional
103 insulin receptors [14-17]. Furthermore, transgenic mouse models have revealed that
104 inducing insulin resistance in different nephron compartments results in a variety of
105 unfavourable renal phenotypes. In the glomerulus, approximately a decade ago it was
106 discovered that human podocytes respond to insulin [14], and express the hallmark
107 components of insulin sensitive cells including the insulin receptor, and key glucose
108 transporters including GLUT4 and GLUT1. To elucidate the biological significance of
109 insulin signalling in these cells, podocyte specific insulin receptor knockout mice were
110 generated [18]. These animals developed albuminuria and a number of features of
111 DN, including increased matrix production, glomerulosclerosis, and GBM thickening,
112 but all in normoglycaemic conditions, suggesting that insulin resistance of this cell *per*
113 *se* may be an important driver in glomerular diseases. Insulin signaling is important in

114 other parts of the nephron. Deletion of the insulin receptor In tubular epithelial cells
115 widespread led to reduced natriuresis and hypertension [16]. Recent studies have
116 begun to dissect out the precise function of the insulin receptor in specific tubular
117 segments. These experiments revealed that loss of the insulin receptor in proximal
118 tubules results in gluconeogenesis [19] while deletion in collecting ducts increased
119 natriuresis and lowered blood pressure [20].

120

121

122 Diabetes provides an ideal environment consisting of increased adiposity,
123 hyperglycaemia, and inflammation which are all important players in promoting
124 podocyte insulin resistance and glomerular dysfunction [17](**Table 1**). A recent study
125 has identified SMAD3 within the inflammation/ fibrosis pathway as an important
126 modulator of podocyte insulin sensitivity in a model of obesity related DN [21]. In this
127 work, mice fed a high fat diet exhibited an increase in kidney and podocyte SMAD3
128 expression levels which resulted in a severely fibrotic kidney; in these conditions
129 SMAD3 knockout animals were protected from kidney damage and fibrosis. In parallel,
130 fatty acid palmitate induces a SMAD3-mediated podocyte insulin resistance paralleled
131 by mitochondrial dysfunction *in vitro*. These responses were exaggerated when
132 animals became albuminuric, and could be rescued by SMAD3 blockade and
133 restoration of podocyte insulin signalling [21]. Other studies have demonstrated that
134 both Nucleotide-binding oligomerization domain containing protein 2 (NOD2)[22] and
135 Toll-like receptor (TLR)[23] mediated-inflammation have an adverse effect on
136 podocyte survival, insulin action, and glomerular permeability to protein. Decreased
137 circulating adiponectin [24, 25], increased free fatty acids (FFA) levels [26], and
138 defects in insulin action promote glomerular cells and podocyte dysfunction, and

139 albuminuria [27, 28]. Epigenetic mechanisms may also be important in determining
140 insulin resistance [29]. This concept has not been studied in great detail to-date, but
141 Kumar and colleagues have shown that insulin resistance induced by palmitate in
142 human urinary podocyte cell lines is associated with an increase in histone H3K36me2
143 and reduced H3K27me3 on the promoter region of FOXO1, a regulator of
144 gluconeogenic genes. This effect was long-lasting and persisted even after the
145 normalisation of palmitate levels [30].

146

147

148 **Glomerular insulin resistance, endoplasmic reticulum (ER) stress and**
149 **autophagy in diabetic glomerulopathy**

150 There are many consequences of insulin resistance within glomeruli, which are likely
151 to contribute to the progression of DN. One key mechanism is changes to the
152 mitochondria and the closely connected ER [31]. Mitochondrial metabolic overload
153 results in increased cellular oxidative stress and ER-stress which leads to the
154 activation of unfolded protein response (UPR)[32]. UPR is a positive cellular response
155 that in its early phase either refolds accumulated unfolded proteins, or degrades
156 unfolded protein by the ubiquitin-proteasome pathway. Misfolded proteins are
157 detected by the ER membrane stress sensors protein kinase RNA-like ER kinase
158 (PERK), inositol-requiring protein 1 α (IRE1 α) and activating transcription factor 6 α
159 (ATF6 α) and its activator X-box binding protein-1 (XBP-1), which, in turn, activates
160 several signalling events and trigger a compensatory response to prevent further
161 accumulation of misfolded protein. However, when the unfolded protein and cellular
162 damage exceeds a threshold, chronic and unresolved stress results in a change from
163 an adaptive to pro-apoptotic responses [32].

164

165 There is some evidence that glucose/oxidative stress-mediated ER stress plays a role
166 in chronic vascular complications in DN [33]. Hyperglycemia, or increased glycation of
167 proteins have been shown to mediate apoptosis partly through increases in ER stress
168 in cultured murine podocytes [34, 35]. Activation of the UPR has also been observed
169 in mouse glomerular mesangial cells exposed to glucose and glucosamine [36], and
170 in kidneys from diabetic rats administered streptozotocin for 16 weeks [37]. Microarray
171 analysis of human biopsies from patients with established DN showed that UPR genes
172 were upregulated proportionally to the severity of diabetic renal lesions [38]. Finally,
173 recent experimental evidence has demonstrated that pharmacological inhibition of ER
174 stress and stabilization of the UPR is beneficial in diabetic glomerulopathy [39].

175

176 Two studies have used transgenic mice to link podocyte insulin resistance with
177 mitochondrial function and ER stress. Ising and colleagues generated a mouse model
178 of podocyte mitochondrial dysfunction by specifically knocking out a key molecule in
179 this cell involved in mitochondrial fusion called prohibitin-2 [40]. This caused a severe
180 phenotype including glomerulosclerosis, renal failure and death at approximately a
181 month of age. They then went on to inhibit both the insulin receptor and IGF-1 receptor
182 (IGF1R) contemporaneously with podocyte-specific knockdown of prohibitin-2.
183 Inhibiting the insulin receptor alone, or in combination with the IGF1R was partially
184 protective and resulted in a significantly longer life span of the mice [40]. This suggests
185 that insulin resistance could reflect a “protective” resetting of cellular substrate
186 utilisation to shield from excess substrate flow to mitochondria with “impaired”
187 respiratory capabilities. In another study, Madhusudhan *et al.* have elegantly shown
188 that under diabetic conditions ER adaptive mechanisms are impaired in the podocyte

189 and that this is exacerbated when the cell is rendered more insulin resistant. Studying
190 human and murine DN they discovered that nephropathy was associated with
191 alterations in the UPR with impairment of the nuclear translocation of XBP-1. Genetic
192 ablation of the transcription factor XBP-1 or activation of ATF6 (downstream of XBP-
193 1) in the podocyte of diabetic mice aggravates DN. Of interest, mice with genetically
194 impaired podocyte insulin signalling exhibited impaired UPR (XBP-1 activation) that
195 was associated with more severe diabetic kidney disease when compared with
196 diabetic controls [41].

197

198 Autophagy, regulated by the mammalian target of rapamycin complex 1 (mTORC1)
199 is, with the UPR, essential to maintain cellular homeostasis and in the context of ER
200 stress contributes towards the elimination of toxic and damaged cellular components
201 [42]. Haploinsufficiency of mTORC1 in podocytes or administration of rapamycin (a
202 mTORC1 inhibitor) resulting in activation of autophagy [43], has been shown to
203 prevent progressive DN [44, 45]. In contrast, mTORC1 activation in podocytes,
204 resulting in inhibition of autophagy, leads to accelerated DN [46]. Loss of insulin
205 sensitivity in cultured podocytes results in suppression of autophagy and addition of
206 rapamycin in these cells attenuates insulin resistance [47].

207

208

209 **Insulin resistance, the glomerular cell cytoskeleton and other mechanisms**

210 Experiments using podocyte cell lines have begun to reveal other downstream targets
211 of insulin resistance which may play a role in DN. Addition of exogenous insulin to
212 human podocytes in culture led to cytoskeletal rearrangement [18], a process which
213 has been pharmacologically targeted using small molecules as a novel therapy for DN

214 [48]. Other studies [49] have identified the cytoskeleton protein septin-7 as playing an
215 important role in the regulation of insulin-mediated translocation of GLUT4 vesicles to
216 the plasma membrane and the control of podocyte glucose transport. Insulin may also
217 modulate calcium signalling in podocytes which has been shown to be important in
218 maintaining cytoskeletal dynamics by altering the expression of canonical transient
219 receptor potential-6 channel-TRPC6 [50] and large-conductance Ca(2+)-activated
220 K(+) channels [51].

221

222 Insulin stimulates the Phosphoinositide 3-kinase (PI3K) pathway and causes AKT
223 activation. In normal physiology, insulin stimulation of podocytes results in AKT
224 phosphorylation (activation), while, in insulin-resistant disease settings such as
225 diabetes, a number of reports have shown an early loss of glomerular AKT
226 phosphorylation whilst AKT signaling is maintained in the tubular compartment of the
227 kidney [28]. AKT exists in three isoforms with AKT2 being located specifically in the
228 podocyte within the kidney [52]. A loss of podocyte AKT2 activation is detrimental
229 when there is chronic kidney disease associated with nephron loss [52]. AKT2 is the
230 major isoform through which insulin signals [53]. It is currently not completely clear if
231 the loss of renal AKT activation is detrimental in the setting of diabetes as a number
232 of studies have shown an increase in AKT phosphorylation in the vasculature in
233 experimental animal models of diabetes [54-58], and pharmacological inhibition of the
234 AKT activation by AS101, may confer renoprotection in diabetes [59]. More work will
235 have to be performed to dissect the exact role of AKT in diabetic kidney disease.

236

237 Insulin can also modulate the renin-angiotensin-aldosterone system, critical for
238 regulating glomerular haemodynamics in DN, by increasing the expression and activity

239 of angiotensin converting enzyme-2 (ACE2)[60]. Further work is required to identify
240 other downstream targets of podocyte insulin signalling ideally using systems biology
241 genomic and proteomic approaches. Candidate molecules altered by insulin signalling
242 might include recently identified genes found to be associated with the early stages of
243 albuminuria in in-bred strains of mice [61].

244

245

246 **Reactive oxygen species and diabetic nephropathy**

247 Over the last decade, an attractive unifying hypothesis has been put forward to explain
248 diabetic microvascular complications; specifically it was postulated that an excess in
249 cellular substrate availability leads to an increase in reactive oxygen species (ROS)
250 which in turn drives vascular complications in DN [62]. However, this unifying
251 hypothesis has been challenged by the negative results of antioxidant-based clinical
252 trials [63], and a new theory of “mitochondrial hormesis” has been proposed [64],
253 whereby the increased mitochondrial superoxide production is considered an indicator
254 of healthy mitochondria and physiologic oxidative phosphorylation.

255

256 Recent research has found a reduction of superoxide in the kidneys of streptozotocin
257 (STZ)-induced diabetic Akita-mice, as assessed by a combination of *in vivo* real-time
258 transcutaneous fluorescence, confocal microscopy, and electron paramagnetic
259 resonance analysis [65]. The authors of this study found that chronic exposure to high
260 glucose levels (as occurs in diabetes) results in disrupted mitochondria, which was
261 associated with a reduced respiration and a lowering in mitochondrial superoxide.
262 Interestingly, genetic or pharmacological correction of mitochondrial dysfunction by

263 improving substrate utilisation was recently found to be renoprotective in a mouse
264 model of tubulointerstitial fibrosis [66].

265

266 From experimental animal studies it appears that increased cytosolic superoxide and
267 other non-mitochondrial sources of ROS generation play a prominent role in diabetic
268 kidney disease and that strategies involving a more targeted (towards specific cellular
269 compartments such as the cytosol) antioxidant approach, may be important to optimize
270 renoprotection in diabetes [67]. Along these lines, human studies have shown that
271 leukocytes obtained from patients with diabetes and DN (when compared with non-
272 diabetics or patients with diabetes without DN) have a reduced maximal respiration
273 and reserve capacity [68, 69] suggesting that chronic metabolic stress in the presence
274 of a reduced mitochondrial function (being this primary or secondary) will manifest with
275 low ATP-linked respiration, low reserve capacity and reduced mitochondrial ROS
276 generation.

277

278 It could be speculated that metabolic stress could initially (early phase) promote an
279 excess production of mitochondrial superoxide [62] that will lead, in a subsequent
280 chronic phase (late phase), towards mitochondrial damage, progressive deterioration
281 in bioenergetic cellular function, reduced ATP synthesis and cell death. Future work
282 will address these questions, and need to evaluate whether cells are able to maintain
283 adequate number of healthy mitochondria which can then burn sufficient substrates for
284 energy production and maintain a “balanced” level of ROS (**Figure 2**).

285

286 AMP-activated protein kinase (AMPK) is a stress-activated kinase that is activated in
287 response to depleting ATP to preserve cell survival under conditions of reduced

288 substrate utilisation. AMPK activation has been involved in mitochondrial biogenesis
289 by leading to increased mitochondrial substrate utilisation and ATP generation, in
290 parallel with stimulation of antioxidant gene expression to ensure an optimal redox
291 balance [70]. Reduced AMPK, as seen in the diabetic kidney of both rodents and
292 humans [65], is associated with reduced catabolic activity (mitochondrial function) [65],
293 and reduced AMPK-mediated inhibition of NADPH oxidase (Nox2) resulting in
294 increased ROS production [71, 72]. Taken together, these results suggest that, in the
295 diabetic kidney, upregulation of AMPK could be therapeutically beneficial in DN [73] to
296 regulate nutrient utilisation and mitochondrial function towards maintenance of an
297 optimum redox balance.

298

299 Overall, more work is required in the DN field to dissect between these opposing
300 theories specifically by examining mitochondrial function and specific ROS moieties
301 both *in vitro* and in tissues.

302

303

304 **Vascular endothelial growth factor-A (VEGFA) and the glycocalyx**

305 Recent studies have shown a connection between insulin resistance and the
306 subsequent production of VEGFA in podocytes [74]. This finding is likely to be
307 important in the setting of DN with many elegant studies using transgenic mice
308 highlighting the importance of podocyte VEGFA levels in the progression of this
309 condition [4]. A new aspect of VEGFA signalling in the glomerulus is potential cross
310 talk between VEGFA secreted from podocytes and the GECs glycocalyx in the setting
311 of diabetes. There is clear evidence that the GECs glycocalyx is lost both systemically
312 and within the diabetic glomerulus, and that this contributes to both cardiovascular and

313 renal complications [6]. Mechanistically there are a number of pathways which led to
314 loss of the glomerular glycocalyx including hyperglycaemia [75], and ROS [76].

315

316 During the early phases of diabetes an increase in VEGFA causes glycocalyx
317 shedding from the GECs. Furthermore, the inhibitory isoform of VEGFA called VEGF-
318 A_{165b} also plays a role in maintaining the GECs glycocalyx in diabetes. Oltean et al.
319 [77] have shown that in diabetic patients with progressive nephropathy, the renal
320 expression of VEGF-A_{165b} is lost. They went on to develop a number of murine models
321 of DN and have shown that genetic overexpression or pharmacological administration
322 of VEGF-A_{165b} to the mouse, acting through VEGF receptor 2 in the GECs, restores
323 damaged glomerular endothelial glycocalyx and improves renal function. VEGF-A_{165b}
324 also improved the permeability of isolated human diabetic glomeruli suggesting the
325 response is conserved across murine and human species [77].

326

327 VEGFA signalling is only one component of a complex system of molecular cross talk
328 between the podocyte and glycocalyx. New insights have revealed that molecules
329 produced by the endothelium can signal to the podocyte and then back to the
330 glomerular glycocalyx. Using transgenic murine models and conditionally immortalised
331 murine podocytes and GECs, Garsen et al have shown that endothelin-1 (ET-1), an
332 endothelial derived vasoconstrictor, is released by the GECs in diabetic conditions and
333 leads to shedding of the glycocalyx [78]. This is prevented by deleting the ET-1
334 receptor specifically in the podocyte. This is therapeutically intriguing as there are ET-
335 1 receptor antagonists that have been shown to ameliorate early microalbuminuric
336 diabetic kidney disease [79]. In the future, therapeutic approaches to maintain the
337 GECs glycocalyx should be explored in more detail (**Figure 3**).

338

339

340 **SGLT2 and kidney disease**

341 Poor glycaemic control and hyperinsulinaemia (at least in the early phase of diabetes)
342 lead to upregulation of SGLT2 expression and proximal tubular SGLT2-mediated
343 sodium-glucose reabsorption [80], which in turns is believed to also contribute to higher
344 blood pressure levels [81]. SGLT2 inhibitors have recently been developed as oral
345 hypoglycaemic agents [82]. The SGLT2 antagonists block the sodium-coupled energy
346 dependent glucose proximal tubular reabsorption resulting in improvement in diabetes
347 control, weight loss and blood pressure lowering. Recent clinical trials have
348 demonstrated a dramatic cardiovascular [83] and renoprotective [84] effect of the
349 SGLT2 inhibitor empaglifozin.

350 The mechanism by which SGLT2 inhibitors exert their renoprotective effects is
351 currently unknown. One possibility is that the improvement in renal disease is
352 secondary to activation of tubuloglomerular feedback, a prime mechanism that
353 determines a reduction in glomerular capillary pressure [85]. A complementary
354 mechanism may be that the inhibition of enhanced tubuli sodium-coupled glucose
355 transport seen in diabetes would result in diminished tubulointerstitial injury and
356 progression of DN [81]. The use of SGLT2 inhibitors in combination with inhibitors of
357 the renin-angiotensin-aldosterone system in patients with diabetes may confer some
358 renoprotection via upregulation of ACE2 and angiotensin 1-7/ 1-9 [86] which retains a
359 vasodilatory, anti-proliferative, anti-inflammatory and anti-oxidative stress effect [87].
360 Inhibition of SGLT2 increased expression and activity in diabetes [85] has been
361 paralleled by activation of AMPK [88], an could promote a favourable renal outcome.

362 In parallel to these “renal mechanisms”, natriuresis and plasma volume contraction
363 paralleled by blood pressure reduction has been also been proposed as a “systemic”
364 renoprotective mechanisms for SGLT2 inhibitors [89](**Figure 4**).

365

366 **Concluding Remarks and Future Perspectives**

367 Glomerular cellular insulin resistance plays an important role in mitochondrial
368 dysfunction-ER stress and the UPR, which contribute to glomerular cell dysfunction
369 and progressive kidney disease. AMPK, with its important role in mitochondrial
370 function, could represent a potential target for treatment in DN; more studies are
371 required to assess the role of AMPK on podocyte biology and the regulation of the
372 glomerular filtration barrier. A link between the tubular compartment and the
373 glomerulus is evident in the pathophysiology of tubular SGLT2-mediated Na-coupled
374 glucose reabsorption in diabetes, however it is not yet completely clear what are the
375 mechanisms underlying these beneficial effects. Future studies will need to better
376 dissect the cellular mechanisms underlying the proposed pathways outlined in this
377 article, specifically focusing on the physiology of the nephron as a whole entity, and
378 by identifying potentially targetable molecules for future treatment.

379

380 **Acknowledgements**

381 LG is supported by Diabetes UK, European Foundation for the Study of Diabetes,
382 Heart Research UK, Diabetes Research Wellness Foundation, and National Institute
383 for Health and Research, Biomedical Research Centre at Guy’s and St Thomas
384 Foundation Trust in partnership with King’s College London.

385 DAL is supported by project grants from Diabetes UK (13/0004763 and 15/0005283),
386 Kidney Research UK (RP36/2015), a Medical Research Council New Investigator

387 Award (MR/J003638/1) and by the National Institute for Health Research Biomedical
388 Research Centre at Great Ormond Street Hospital for Children NHS Foundation Trust
389 and University College London.

390 RJMC is supported by an MRC Senior Clinical Fellowship MR/K010492/1, Kidney
391 Research UK, Wellcome Trust, and the European Union.

392

393

394 **TABLE 1**

395 Diabetes results in inflammation, increased adiposity and chronic hyperglycaemia
 396 which drive podocyte insulin resistance resulting in disruption to podocytes and the
 397 glomerulus. (NOD2: Nucleotide-binding oligomerization domain containing protein 2,
 398 TLR: Toll-like receptor, SMAD: vertebrate homologues of *Sma* and *Mad*; FFAs: free
 399 fatty acids; SHP-1: Src homology-2 domain-containing phosphatase-1)

400

Diabetes related phenotypes	Molecular mechanisms	Glomerular phenotype	REF #
Chronic inflammation	Increased NOD2	Increased pro-inflammatory responses and impaired insulin signaling	[22]
	Increased TLR	Podocyte inflammation and insulin resistance	[23]
	Increased SMAD	Mitochondrial dysfunction and insulin resistance in podocytes	[21]
Obesity	Decreased adiponectin	Albuminuria and increased oxidative stress in podocytes	[24]
	Increased FFAs	Inhibition of insulin-stimulated glucose uptake in human podocytes	[26]
Elevated blood sugar	Increased SHP-1	Podocyte insulin resistance and detachment	[27]
	Ubiquitination and degradation of components of insulin signaling pathway	Diabetic glomerulopathy and albuminuria	[28]

401

402 **Figure legends:**

403

404 **Figure 1: Schematic structure of a normal and diabetic glomeruli.**

405 (A) Schematic representation of a normal glomerular structure. (B) The major
406 glomerular structural changes occurring in diabetic glomerulopathy. Note the
407 extensive mesangial expansion, the thickening of the glomerular basement membrane
408 (GBM), the detachment of podocyte, and the impairment in the glycocalyx and
409 glomerular endothelial cells (GECs).

410

411 **Figure 2: Hypothetical shift of superoxide level imbalance in diabetic**
412 **complications.**

413 Acute (early phase) exposure of cells to elevated glucose levels results in upregulation
414 of glucose oxidation with pyruvate-mediated stimulation of the tricarboxylic acid (TCA)
415 cycle with increased production of electron donors (NADH, FADH₂) that, via the
416 electron transport chain, will results in an excess generation of superoxide (O₂⁻). Cells
417 chronically exposed to elevated glucose levels (late phase) will result in reduction in
418 the availability of acetyl-CoA (secondary to inhibition of pyruvate dehydrogenase
419 activity) for the mitochondria resulting in reduced electron transport chain activity, a
420 fall in mitochondrial ATP production, less mitochondria superoxide production and
421 cellular dysfunction.

422

423 **Figure 3: Glomerular cell cross-talk and glycocalyx.**

424 Transmission electron microscopy image of the glomerular filtration barrier (podocyte
425 glomerular basement membrane (GBM), glomerular endothelial cells (GEC), and
426 glycocalyx) highlighting how molecules produced by the podocytes and endothelium

427 (via the podocyte) can signal to the glomerular glycocalyx. Recently identified key
428 molecules such as VEGF-A_{165b}, VEGF-C, and angiopoietin-1 (ANGPT1) confer a
429 beneficial effect (green arrows) towards glycocalyx maintenance. Conversely VEGF-
430 A₁₆₅ and Endothelin (secreted by GECs and signals to the Endothelin-1 receptor in the
431 podocyte causing this cell to release heparanase, which then acts on the glomerular
432 glycocalyx to cleave heparin sulphate) promote shedding of the GECs glycocalyx (red
433 arrows).

434

435 **Figure 4: Proposed SGLT2 inhibition-mediated renoprotective mechanisms.**

436 SGLT2 inhibition blocks sodium-glucose coupled glucose reabsorption at the S1 S2
437 segment of the proximal tubule. The net result is loss of glucose and sodium (the latter
438 especially in patients on renin angiotensin aldosterone blockade) in the urine, with
439 secondary weight loss, improvement in glycaemic control, blood pressure fall, and
440 plasma volume contraction. These effects confer cardiac and renal protection in
441 patients with diabetes. (ACE2: angiotensin converting enzyme 2)

442

References:

443
444

445 1 Gnudi, L., Gentile, G., Ruggenenti, P. (2016) The patient with diabetes mellitus. In *Oxford*
446 *Textbook of Clinical Nephrology* (Turner, N., Lamiere, N., Goldsmith, D.J., Wineearls, C.G.,
447 Himmelfarb, J., Remuzzi, G., ed), pp. 1199-1247, Oxford University Press

448 2 Benzing, T. (2004) Signaling at the slit diaphragm. *J Am Soc Nephrol* 15, 1382-1391

449 3 Zhu, J., *et al.* (2008) Nephrin mediates actin reorganization via phosphoinositide 3-kinase
450 in podocytes. *Kidney Int* 73, 556-566

451 4 Gnudi, L., *et al.* (2015) Vascular growth factors play critical roles in kidney glomeruli. *Clin*
452 *Sci (Lond)* 129, 1225-1236

453 5 Haraldsson, B., *et al.* (2008) Properties of the glomerular barrier and mechanisms of
454 proteinuria. *Physiol Rev.* 88, 451-487

455 6 Salmon, A.H., *et al.* (2012) Loss of the endothelial glycocalyx links albuminuria and
456 vascular dysfunction. *J Am Soc Nephrol* 23, 1339-1350

457 7 Deckert, T., *et al.* (1989) Albuminuria reflects widespread vascular damage. The Steno
458 hypothesis. *Diabetologia* 32, 219-226

459 8 Orchard, T.J., *et al.* (2002) Nephropathy in type 1 diabetes: a manifestation of insulin
460 resistance and multiple genetic susceptibilities? Further evidence from the Pittsburgh
461 Epidemiology of Diabetes Complication Study. *Kidney Int* 62, 963-970

462 9 Karalliedde, J. and Gnudi, L. (2016) Diabetes mellitus, a complex and heterogeneous
463 disease, and the role of insulin resistance as a determinant of diabetic kidney disease.
464 *Nephrol Dial Transplant* 31, 206-213

465 10 Sasson, A.N. and Cherney, D.Z. (2012) Renal hyperfiltration related to diabetes mellitus
466 and obesity in human disease. *World J Diabetes* 3, 1-6

467 11 Gnudi, L., *et al.* (2007) Mechanical forces in diabetic kidney disease: a trigger for
468 impaired glucose metabolism. *J.Am.Soc.Nephrol.* 18, 2226-2232

469 12 Trevisan, R., *et al.* (1998) Enhanced responsiveness of blood pressure to sodium intake
470 and to angiotensin II is associated with insulin resistance in IDDM patients with
471 microalbuminuria. *Diabetes* 47, 1347-1353

472 13 Vedovato, M., *et al.* (2004) Effect of sodium intake on blood pressure and albuminuria in
473 Type 2 diabetic patients: the role of insulin resistance. *Diabetologia* 47, 300-303

474 14 Coward, R.J., *et al.* (2005) The human glomerular podocyte is a novel target for insulin
475 action. *Diabetes* 54, 3095-3102

476 15 Butlen, D., *et al.* (1988) Insulin receptors along the rat nephron: [125I] insulin binding in
477 microdissected glomeruli and tubules. *Pflugers Arch* 412, 604-612

478 16 Tiwari, S., *et al.* (2008) Impaired sodium excretion and increased blood pressure in mice
479 with targeted deletion of renal epithelial insulin receptor. *Proc Natl Acad Sci U S A* 105,
480 6469-6474

- 481 17 Lay, A. and Coward, R.J. (2014) Recent advances in our understanding of insulin
482 signalling to the podocyte. *Nephrol Dial Transplant* 29, 1127-1133
- 483 18 Welsh, G.I., *et al.* (2010) Insulin signaling to the glomerular podocyte is critical for normal
484 kidney function. *Cell Metab* 12, 329-340
- 485 19 Tiwari, S., *et al.* (2013) Deletion of the insulin receptor in the proximal tubule promotes
486 hyperglycemia. *J Am Soc Nephrol* 24, 1209-1214
- 487 20 Li, L., *et al.* (2013) Reduced ENaC activity and blood pressure in mice with genetic
488 knockout of the insulin receptor in the renal collecting duct. *Am J Physiol Renal Physiol* 304,
489 F279-288
- 490 21 Sun, Y.B., *et al.* (2015) Smad3 deficiency protects mice from obesity-induced podocyte
491 injury that precedes insulin resistance. *Kidney Int* 88, 286-298
- 492 22 Du, P., *et al.* (2013) NOD2 promotes renal injury by exacerbating inflammation and
493 podocyte insulin resistance in diabetic nephropathy. *Kidney Int* 84, 265-276
- 494 23 Cha, J.J., *et al.* (2013) Renal protective effects of toll-like receptor 4 signaling blockade in
495 type 2 diabetic mice. *Endocrinology* 154, 2144-2155
- 496 24 Sharma, K., *et al.* (2008) Adiponectin regulates albuminuria and podocyte function in
497 mice. *J Clin. Invest* 118, 1645-1656
- 498 25 Sweiss, N. and Sharma, K. (2014) Adiponectin effects on the kidney. *Best Pract Res Clin*
499 *Endocrinol Metab* 28, 71-79
- 500 26 Lennon, R., *et al.* (2009) Saturated fatty acids induce insulin resistance in human
501 podocytes: implications for diabetic nephropathy. *Nephrol Dial Transplant* 24, 3288-3296
- 502 27 Drapeau, N., *et al.* (2013) Expression of SHP-1 induced by hyperglycemia prevents
503 insulin actions in podocytes. *Am J Physiol Endocrinol Metab* 304, E1188-1198
- 504 28 Mima, A., *et al.* (2011) Glomerular-specific protein kinase C-beta-induced insulin receptor
505 substrate-1 dysfunction and insulin resistance in rat models of diabetes and obesity. *Kidney*
506 *Int* 79, 883-896
- 507 29 Duque-Guimaraes, D.E. and Ozanne, S.E. (2013) Nutritional programming of insulin
508 resistance: causes and consequences. *Trends Endocrinol Metab* 24, 525-535
- 509 30 Kumar, S., *et al.* (2016) Fatty acid induced metabolic memory involves alterations in renal
510 histone H3K36me2 and H3K27me3. *Mol Cell Endocrinol* 422, 233-242
- 511 31 Kornmann, B., *et al.* (2009) An ER-mitochondria tethering complex revealed by a
512 synthetic biology screen. *Science* 325, 477-481
- 513 32 Hetz, C. (2012) The unfolded protein response: controlling cell fate decisions under ER
514 stress and beyond. *Nature reviews. Molecular cell biology* 13, 89-102
- 515 33 Zhuang, A. and Forbes, J.M. (2014) Stress in the kidney is the road to pERdition: is
516 endoplasmic reticulum stress a pathogenic mediator of diabetic nephropathy? *The Journal of*
517 *endocrinology* 222, R97-111
- 518 34 Cao, Y., *et al.* (2014) Role of endoplasmic reticulum stress in apoptosis of differentiated
519 mouse podocytes induced by high glucose. *Int J Mol Med* 33, 809-816

- 520 35 Chen, Y., *et al.* (2008) Effect of taurine-conjugated ursodeoxycholic acid on endoplasmic
521 reticulum stress and apoptosis induced by advanced glycation end products in cultured
522 mouse podocytes. *Am J Nephrol* 28, 1014-1022
- 523 36 Cheng, D.W., *et al.* (2006) An analysis of high glucose and glucosamine-induced gene
524 expression and oxidative stress in renal mesangial cells. *Arch Physiol Biochem* 112, 189-
525 218
- 526 37 Liu, G., *et al.* (2008) Apoptosis induced by endoplasmic reticulum stress involved in
527 diabetic kidney disease. *Biochem Biophys Res Commun* 370, 651-656
- 528 38 Lindenmeyer, M.T., *et al.* (2008) Proteinuria and hyperglycemia induce endoplasmic
529 reticulum stress. *J Am Soc Nephrol* 19, 2225-2236
- 530 39 Cao, A.L., *et al.* (2016) Ursodeoxycholic acid and 4-phenylbutyrate prevent endoplasmic
531 reticulum stress-induced podocyte apoptosis in diabetic nephropathy. *Lab Invest*
- 532 40 Ising, C., *et al.* (2015) Inhibition of insulin/IGF-1 receptor signaling protects from
533 mitochondria-mediated kidney failure. *EMBO Mol Med* 7, 275-287
- 534 41 Madhusudhan, T., *et al.* (2015) Defective podocyte insulin signalling through p85-XBP1
535 promotes ATF6-dependent maladaptive ER-stress response in diabetic nephropathy. *Nature*
536 *communications* 6, 6496
- 537 42 Kroemer, G., *et al.* (2010) Autophagy and the integrated stress response. *Mol Cell* 40,
538 280-293
- 539 43 Kim, J., *et al.* (2011) AMPK and mTOR regulate autophagy through direct
540 phosphorylation of Ulk1. *Nat Cell Biol* 13, 132-141
- 541 44 Godel, M., *et al.* (2011) Role of mTOR in podocyte function and diabetic nephropathy in
542 humans and mice. *J Clin Invest* 121, 2197-2209
- 543 45 Xiao, T., *et al.* (2014) Rapamycin promotes podocyte autophagy and ameliorates renal
544 injury in diabetic mice. *Mol Cell Biochem* 394, 145-154
- 545 46 Inoki, K., *et al.* (2011) mTORC1 activation in podocytes is a critical step in the
546 development of diabetic nephropathy in mice. *J Clin Invest* 121, 2181-2196
- 547 47 Xu, Y., *et al.* (2016) Autophagy downregulation contributes to insulin resistance mediated
548 injury in insulin receptor knockout podocytes in vitro. *PeerJ* 4, e1888
- 549 48 Schiffer, M., *et al.* (2015) Pharmacological targeting of actin-dependent dynamin
550 oligomerization ameliorates chronic kidney disease in diverse animal models. *Nat Med* 21,
551 601-609
- 552 49 Wasik, A.A., *et al.* (2012) Septin 7 forms a complex with CD2AP and nephrin and
553 regulates glucose transporter trafficking. *Mol Biol Cell* 23, 3370-3379
- 554 50 Kim, E.Y., *et al.* (2012) Insulin increases surface expression of TRPC6 channels in
555 podocytes: role of NADPH oxidases and reactive oxygen species. *Am J Physiol Renal*
556 *Physiol* 302, F298-307
- 557 51 Kim, E.Y. and Dryer, S.E. (2011) Effects of insulin and high glucose on mobilization of
558 slo1 BKCa channels in podocytes. *J Cell Physiol* 226, 2307-2315

559 52 Canaud, G., *et al.* (2013) AKT2 is essential to maintain podocyte viability and function
560 during chronic kidney disease. *Nat Med* 19, 1288-1296

561 53 George, S., *et al.* (2004) A family with severe insulin resistance and diabetes due to a
562 mutation in AKT2. *Science* 304, 1325-1328

563 54 Zdychova, J. and Komers, R. (2005) Emerging role of Akt kinase/protein kinase B
564 signaling in pathophysiology of diabetes and its complications. *Physiol Res* 54, 1-16

565 55 Wu, D., *et al.* (2009) PKC-beta1 mediates glucose-induced Akt activation and TGF-beta1
566 upregulation in mesangial cells. *J Am Soc Nephrol* 20, 554-566

567 56 Kato, M., *et al.* (2006) Role of the Akt/FoxO3a pathway in TGF-beta1-mediated
568 mesangial cell dysfunction: a novel mechanism related to diabetic kidney disease. *J Am Soc
569 Nephrol* 17, 3325-3335

570 57 Xin, X., *et al.* (2005) Glucose-induced Akt1 activation mediates fibronectin synthesis in
571 endothelial cells. *Diabetologia* 48, 2428-2436

572 58 Kim, S.Y., *et al.* (2009) Role of kidney ADP-ribosyl cyclase in diabetic nephropathy. *Am J
573 Physiol Renal Physiol* 296, F291-297

574 59 Shemesh, Il, *et al.* (2014) AS101 prevents diabetic nephropathy progression and
575 mesangial cell dysfunction: regulation of the AKT downstream pathway. *PLoS One* 9,
576 e114287

577 60 Riera, M., *et al.* (2014) Effect of insulin on ACE2 activity and kidney function in the non-
578 obese diabetic mouse. *PLoS One* 9, e84683

579 61 Long, D.A., *et al.* (2013) Albuminuria is associated with too few glomeruli and too much
580 testosterone. *Kidney Int*

581 62 Brownlee, M. (2001) Biochemistry and molecular cell biology of diabetic complications.
582 *Nature* 414, 813-820

583 63 Forbes, J.M., *et al.* (2008) Oxidative stress as a major culprit in kidney disease in
584 diabetes. *Diabetes* 57, 1446-1454

585 64 Sharma, K. (2015) Mitochondrial hormesis and diabetic complications. *Diabetes* 64, 663-
586 672

587 65 Dugan, L.L., *et al.* (2013) AMPK dysregulation promotes diabetes-related reduction of
588 superoxide and mitochondrial function. *J Clin Invest* 123, 4888-4899

589 66 Kang, H.M., *et al.* (2015) Defective fatty acid oxidation in renal tubular epithelial cells has
590 a key role in kidney fibrosis development. *Nat Med* 21, 37-46

591 67 Forbes, J.M. and Cooper, M.E. (2013) Mechanisms of diabetic complications.
592 *Physiological reviews* 93, 137-188

593 68 Czajka, A., *et al.* (2015) Altered Mitochondrial Function, Mitochondrial DNA and Reduced
594 Metabolic Flexibility in Patients With Diabetic Nephropathy. *EBioMedicine* 2, 499-512

595 69 Chacko, B.K., *et al.* (2015) The Bioenergetic Health Index is a sensitive measure of
596 oxidative stress in human monocytes. *Redox biology* 8, 43-50

597 70 Hardie, D.G., *et al.* (2012) AMPK: a nutrient and energy sensor that maintains energy
598 homeostasis. *Nature reviews. Molecular cell biology* 13, 251-262

599 71 Sedeek, M., *et al.* (2010) Critical role of Nox4-based NADPH oxidase in glucose-induced
600 oxidative stress in the kidney: implications in type 2 diabetic nephropathy. *Am J Physiol*
601 *Renal Physiol* 299, F1348-1358

602 72 Eid, A.A., *et al.* (2010) AMP-activated protein kinase (AMPK) negatively regulates Nox4-
603 dependent activation of p53 and epithelial cell apoptosis in diabetes. *J Biol Chem* 285,
604 37503-37512

605 73 Al-Rasheed, N.M., *et al.* (2015) Renoprotective Effects of Fenofibrate via Modulation of
606 LKB1/AMPK mRNA Expression and Endothelial Dysfunction in a Rat Model of Diabetic
607 Nephropathy. *Pharmacology* 95, 229-239

608 74 Hale, L.J., *et al.* (2013) Insulin directly stimulates VEGF-A production in the glomerular
609 podocyte. *Am J Physiol Renal Physiol* 305, F182-188

610 75 Singh, A., *et al.* (2011) High glucose causes dysfunction of the human glomerular
611 endothelial glycocalyx. *Am J Physiol Renal Physiol* 300, F40-48

612 76 Singh, A., *et al.* (2013) Reactive oxygen species modulate the barrier function of the
613 human glomerular endothelial glycocalyx. *PLoS One* 8, e55852

614 77 Oltean, S., *et al.* (2014) Vascular Endothelial Growth Factor-A165b Is Protective and
615 Restores Endothelial Glycocalyx in Diabetic Nephropathy. *J Am Soc Nephrol*

616 78 Garsen, M., *et al.* (2016) Endothelin-1 Induces Proteinuria by Heparanase-Mediated
617 Disruption of the Glomerular Glycocalyx. *J Am Soc Nephrol*

618 79 de Zeeuw, D., *et al.* (2014) The endothelin antagonist atrasentan lowers residual
619 albuminuria in patients with type 2 diabetic nephropathy. *J Am Soc Nephrol* 25, 1083-1093

620 80 Rahmoune, H., *et al.* (2005) Glucose transporters in human renal proximal tubular cells
621 isolated from the urine of patients with non-insulin-dependent diabetes. *Diabetes* 54, 3427-
622 3434

623 81 Vallon, V. and Thomson, S.C. (2012) Renal function in diabetic disease models: the
624 tubular system in the pathophysiology of the diabetic kidney. *Annual review of physiology* 74,
625 351-375

626 82 Ferrannini, E. and Solini, A. (2012) SGLT2 inhibition in diabetes mellitus: rationale and
627 clinical prospects. *Nat Rev Endocrinol* 8, 495-502

628 83 Zinman, B., *et al.* (2015) Empagliflozin, Cardiovascular Outcomes, and Mortality in Type
629 2 Diabetes. *N Engl J Med* 373, 2117-2128

630 84 Wanner, C., *et al.* (2016) Empagliflozin and Progression of Kidney Disease in Type 2
631 Diabetes. *N Engl J Med*

632 85 Vallon, V. (2015) The mechanisms and therapeutic potential of SGLT2 inhibitors in
633 diabetes mellitus. *Annu Rev Med* 66, 255-270

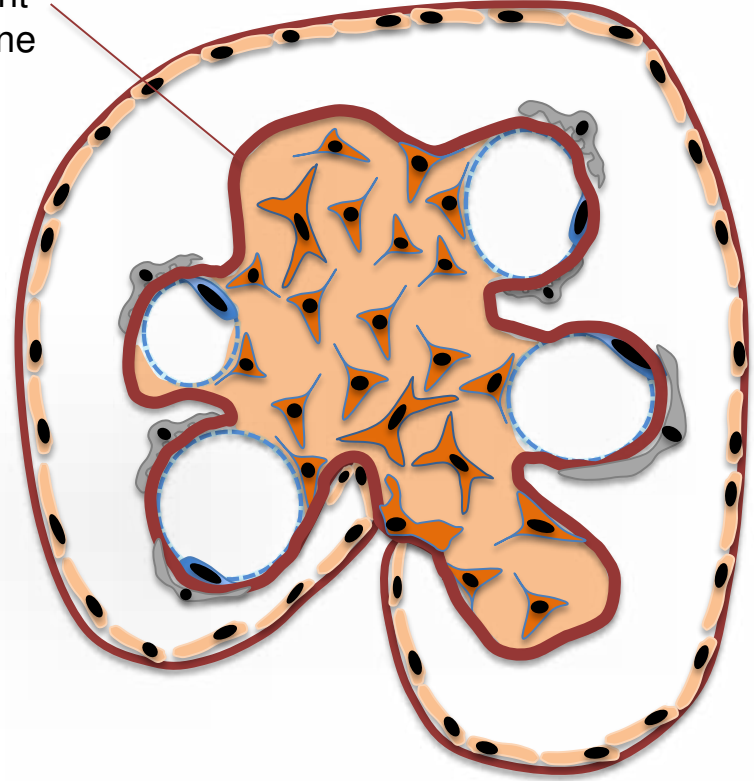
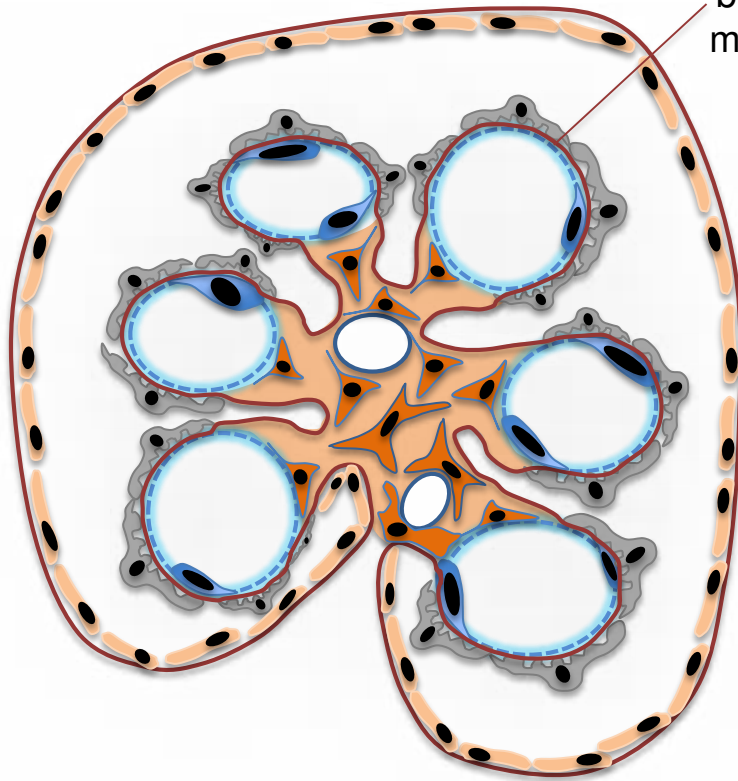
634 86 Tikellis, C., *et al.* (2008) ACE2 deficiency modifies renoprotection afforded by ACE
635 inhibition in experimental diabetes. *Diabetes* 57, 1018-1025

- 636 87 Burrell, L.M., *et al.* (2004) ACE2, a new regulator of the renin-angiotensin system. *Trends*
637 *Endocrinol Metab* 15, 166-169
- 638 88 Hawley, S.A., *et al.* (2016) The Na⁺/glucose co-transporter inhibitor canagliflozin
639 activates AMP-activated protein kinase by inhibiting mitochondrial function and increasing
640 cellular AMP levels. *Diabetes*
- 641 89 Rajasekeran, H., *et al.* (2016) Sodium-glucose cotransporter 2 inhibition and
642 cardiovascular risk reduction in patients with type 2 diabetes: the emerging role of
643 natriuresis. *Kidney Int* 89, 524-526
- 644

A

B

glomerular
basement
membrane



podocyte



Mesangium

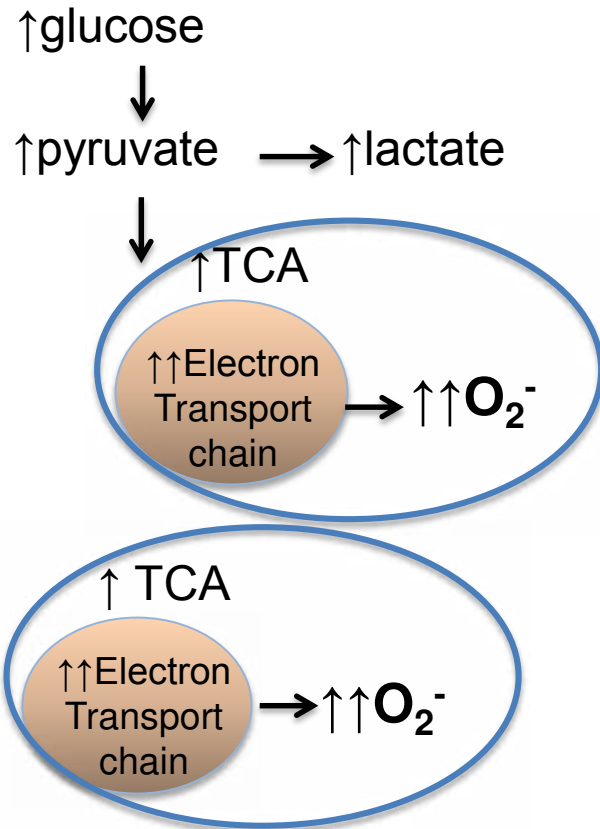


GECs



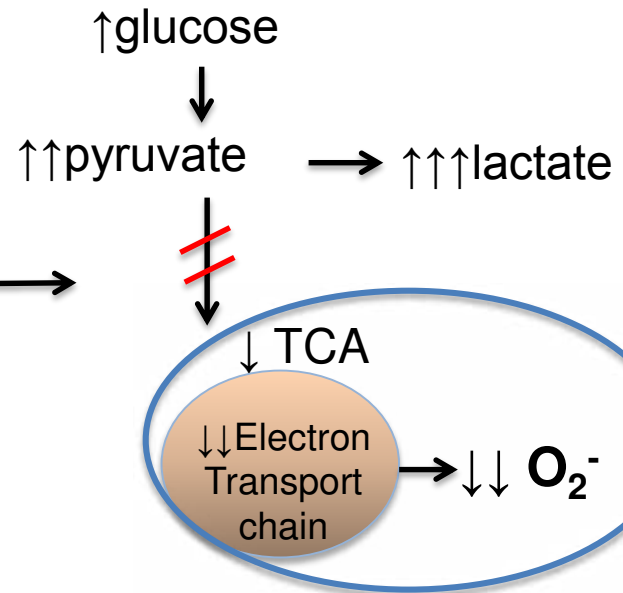
glycocalyx

Elevated superoxide
with high glucose

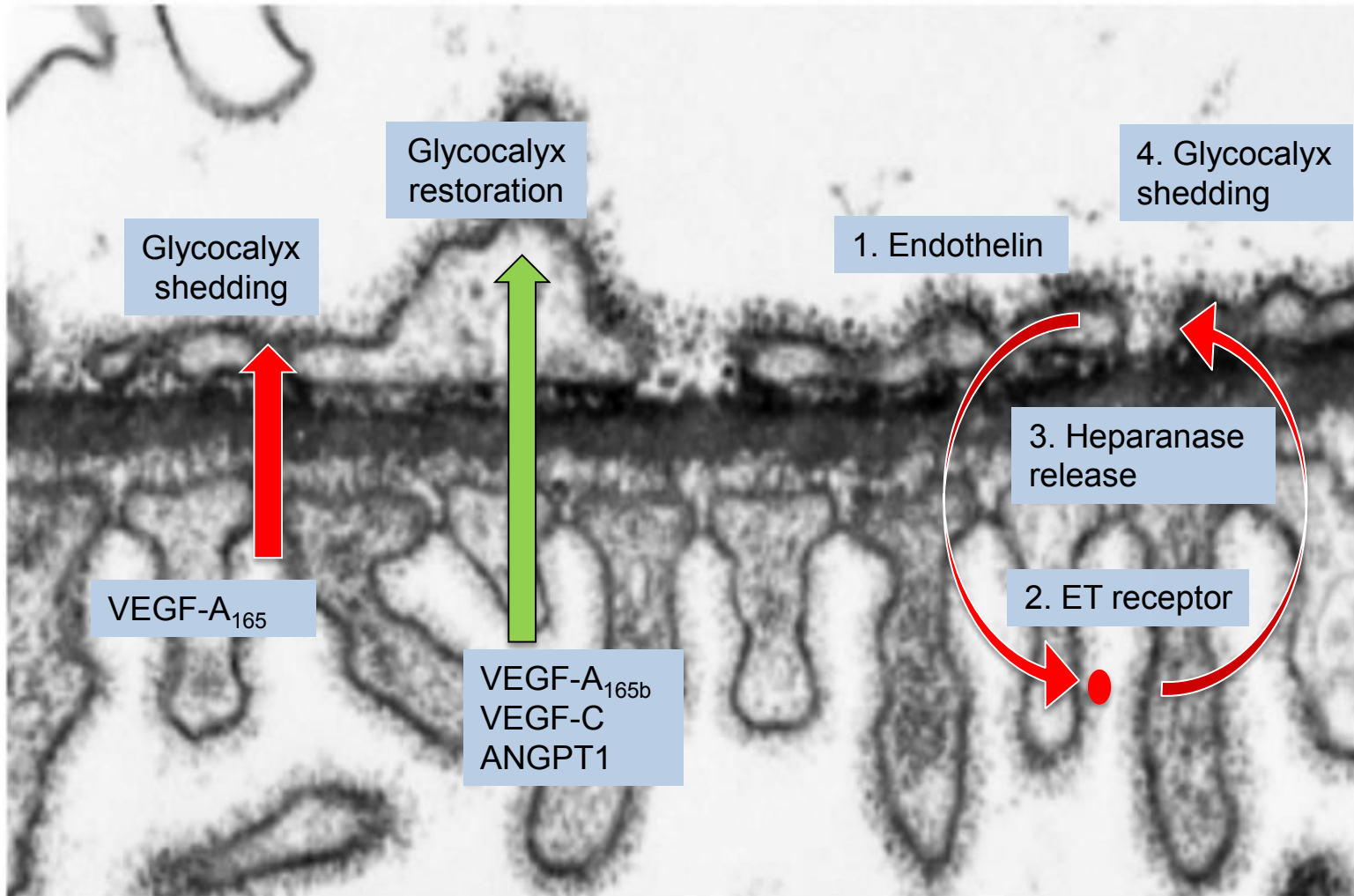


Early phase

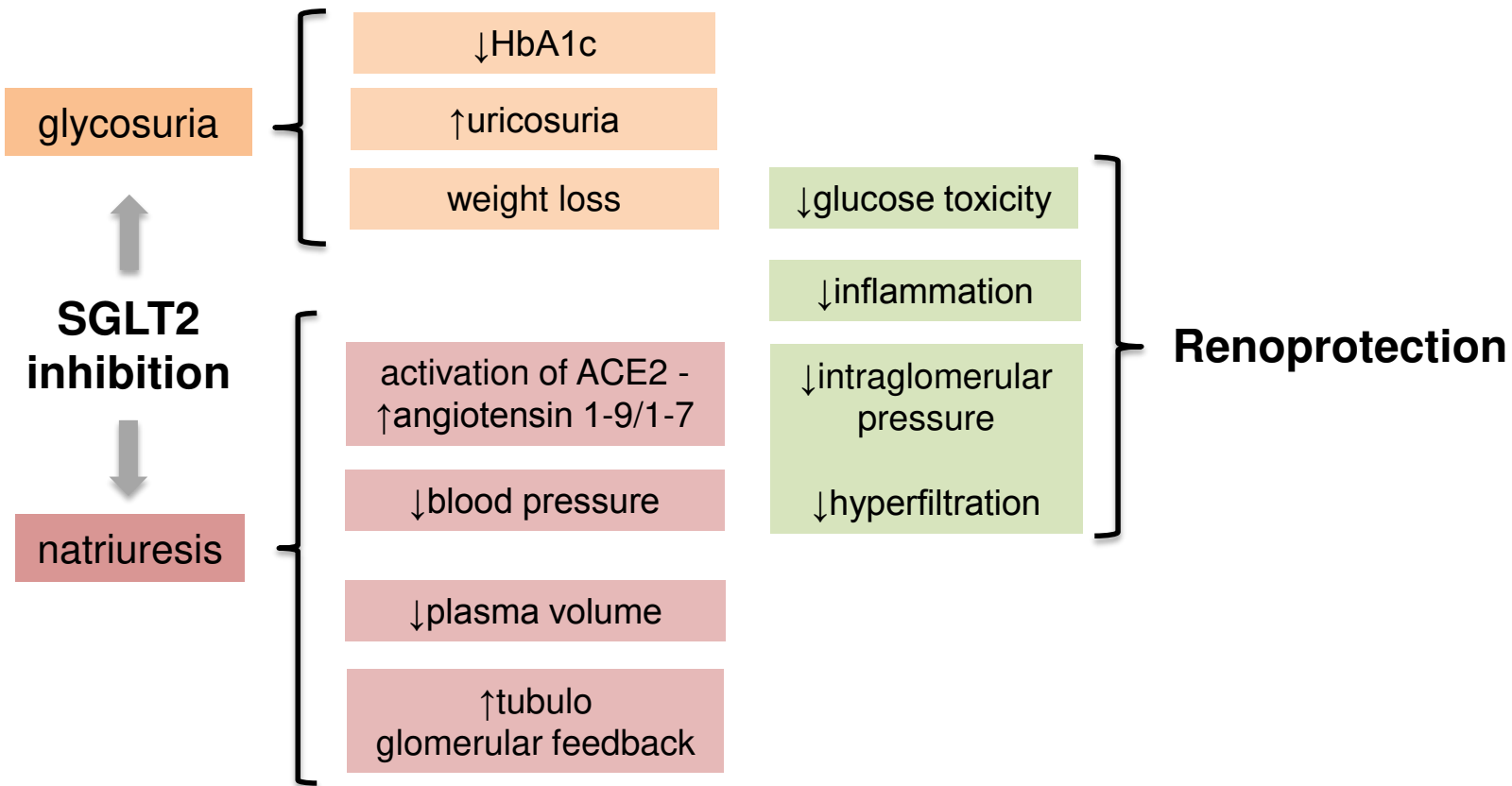
Reduced superoxide
with high glucose



Late phase



← Glycocalyx
← GECs
← GBM
← Podocyte



OUTSTANDING QUESTIONS BOX

- What are the main pathway/s that link insulin action, mitochondrial function and UPR?
- What are the mitochondrial-driven mechanisms that predispose towards faster kidney disease progression in diabetes? Is there an alteration in the mitochondria driven UPR-mediated response towards cell survival or is it a primary alteration in UPR response?
- Does AMPK, with its important role as a regulator of nutrient utilisation and mitochondrial function, represent a real answer to diabetes mediated ER-stress mitochondria dysfunction, UPR, and, if so, what are the mechanisms?
- Could targeting the glycocalyx be a new therapeutic approach for diabetic nephropathy? What are the important molecular signals from the podocyte and endothelium which regulate the glycocalyx?
- How does SGLT2 inhibition confer reno-protection? Is it about SGLT2-driven sodium and volume loss (systemic effect) or tubuloglomerular feedback and inflammation (intrarenal effect)? Are these mechanisms behind the renoprotective effects of these drugs?

TRENDS BOX:

- Insulin resistance is a key mechanism for diabetic glomerulopathy.
- Disruption in the molecular communication between glomerular podocytes and endothelia is critical in the progression of diabetic nephropathy.
- Raised (but not too elevated) mitochondrial superoxide cellular levels in parallel with healthy mitochondria are protective against progression of diabetic kidney disease.
- A reduction in maximal mitochondrial respiration and reserve capacity could represent an important driving force for kidney disease progression in diabetes.
- Inhibition of SGLT2-mediated sodium-coupled glucose transport confers renoprotection of similar magnitude of inhibitors of the renin-angiotensin-aldosterone system.