BE PART OF MAKING A SHIFT IN TYPE 2 DIABETES

With an early shift in treatment you could help reduce the risk factors associated with type 2 diabetes and help your patients avoid long-term complications.[1–3]

Shift the trajectory of type 2 diabetes

Early and intensive HbA_{1c} control, weight loss and reduction of risk factors are essential to prevent long-term complications associated with type 2 diabetes.[4–6]

With uncontrolled HbA_{1c} a 1% drop could make all the difference.

The closer people living with type 2 diabetes are to their target HbA_{1c}, the lower the risk of complications in the future. Observational and clinical trial analyses suggest that a 1% reduction in HbA_{1c} has the potential to reduce the risk of complications and prevent deaths related to diabetes.[4,7]

You play an important role in type 2 diabetes management by making sure your patients are getting the treatment that is right for them and the advice they need to stay on track.

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*To learn how an early **shift** in treatment could lead to better health outcomes for your patients,* ***visit Novo Nordisk***

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LETTER TO THE EDITOR

Letter regarding the article "Hypocapnia is an independent predictor of in-hospital mortality in acute heart failure"

The role of hypocapnia in acute heart failure (AHF) remains poorly understood. Tang and colleagues found that hypocapnia was associated with worse renal and cardiac function and a higher in-hospital, all-cause mortality in a cohort of patients with AHF.[1] Respiratory rate was similar (approximately 20 breaths per minute; $P = 0.857$) for those with or without hypocapnia, suggesting that increased ventilation was not responsible for hypocapnia. Interestingly, the authors report that patients receiving SGLT2 inhibitors were less likely to have hypocapnia ($P = 0.032$); a difference that remained even after a propensity score matched analysis ($P = 0.014$).

Sodium/glucose cotransporter 2 inhibitors reduce glucose utilization in favour of a higher proportion of energy derived from beta-oxidation of fatty acids.[2] Glucose is a six-carbon molecule rather than a longer carbon-chain fatty-acid. Glucose oxidation requires less oxygen, produces less CO_2 but also produce less ATP, with an even greater reduction of CO_2 and ATP production if the process occurs in anaerobiosis, which leads to increased lactate production. In contrast, fatty-acid oxidation requires more oxygen, produces more CO_2, but generates at least three times more ATP molecules than glucose oxidation, depending on the length of the long-chain fatty acid (LCFA). In fact, it is possible to predict how many ATP molecules can be obtained from a LCFA depending on the length and saturation of the fatty-acid. For a saturated, even-numbered fatty acid of 16 carbons (e.g. palmitic acid), the formula {ATP = [7 · (C-2)] + 8} provides an estimate of 106 ATP molecules produced.[3] Ketones are a by-product of and signal for LCFA metabolism, but ketones might also be an efficient substrate for energy production in failing cardiac myocytes[2].

The stoichiometry of the two chemical reactions to produce energy from glucose and palmitic acid are shown:

Glucose oxidation:

- during *aerobiosis*: $\mathbf{C_6}H_{12}O_2 + 6\ O_2 -\ >\ \underline{\mathbf{6\ CO_2}} + \underline{\mathbf{36\ ATP}} + 6\ H_2O$
- during *anaerobiosis*: $\mathbf{C_6}H_{12}O_2 -\ >\ \underline{\mathbf{2\ ATP + 2\ Lactate}}$

Fatty acid oxidation (e.g. 16 C):

- $\mathbf{C_{16}}H_{12}O_2 + 23\ O_2$ - > $\underline{\mathbf{16\ CO_2}} + \underline{\mathbf{106\ ATP}} + H_2O$

With worsening haemodynamics, less oxygen is delivered to the tissues in combination with a metabolic reprogramming of the failing cardiomyocyte, whereby aerobic or anaerobic glucose utilization displaces fatty acid oxidation as the energy supply.[2] If so, lower pCO_2 and higher lactate should reflect less ATP and lead to worse cardiac and renal function and worse outcomes. Moreover, lower pCO_2 may conspire with lower pO_2 levels[4] to feed a vicious cycle of increased glycolysis.

Gliflozins, by increasing fatty acids oxidation,[2] should increase pCO_2, which might improve outcome, consistent with the authors' findings. Hypocapnia may be a useful marker of the metabolic substrate and explain, at least in part, the mechanism of action and benefits of gliflozins. Further research to understand the prevalence and significance of hypocapnia in other clinical settings and any interaction with the benefits of sodium/glucose cotransporter 2 inhibitor is warranted.

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