Novel treatment (new drug/intervention; established drug/procedure in new situation)

Towards creating a superstimulus to normalise glucose metabolism in the prediabetic: a case-study in the feast-famine and activity-rest cycle

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Summary

We live in a time of plenty. During evolution, periods of hunger and simultaneously high activity levels would combine giving a stimulus which is absent from modern lifestyles. This is potentially connected with abnormal glucose metabolism. It was hypothesised that simultaneous fasting and aggressive aerobic neuromuscular electrical stimulation (NMES) exercise, until metabolic exhaustion, may be an acceptable modern equivalent. A healthy subject fasted for 44 h (water allowed) during which he undertook three aerobic NMES sessions at $>50\% \text{VO}_{2\text{max}}$; heart rate >160 bpm. Metabolic gas analysis of a comparable session in the non-fasting state showed 100% carbohydrate substrate utilisation. With fasting the NMES exercise consumed mostly fat—up to 100% fat utilisation at 42 h. This clear shift away from using carbohydrate as a substrate and hypoglycaemia may indicate that carbohydrate stores are nearly depleted. The authors postulate that this may constitute a metabolic super stimulus mimicking the famine-activity periods of our ancestors.

BACKGROUND

Chakravarthy and Booth put forward a novel concept ‘that, over the millennia, *Homo sapiens* have evolved metabolic pathways that oscillate to support and coincide with the cycles of feast-famine and of physical activity-rest’.¹ Hunger/famine and activity ‘essentially simultaneous’ are an important part of that cycle, they argue, to help prevent metabolic derangements such as obesity and type 2 diabetes.

While type 2 diabetes is often thought of as a chronic, progressive condition arising out of impaired glucose tolerance or raised fasting glucose this bleak picture is not universally true. Lifestyle modifications may halt the progression and sometimes even reverse abnormalities,² exercise and weight loss improve insulin sensitivity and a short course of medication can sometimes give the newly diagnosed a ‘honeymoon’ from diabetes. Fasting has been reported since the siege of Paris in 1870 to stop glycosuria.³ Each of these interventions may be thought of as a stimulus tipping the scales of metabolism back towards normality.

One of the problems with lifestyle interventions is that, by definition, they require long-term adherence. Any prospect of a short intervention that delivered a superstimulus would be attractive and worth researching. While not negating the need for long-term lifestyle changes it may kick-start a program and aim to, at least temporarily, normalise glucose metabolism. We hypothesised that a 1 or 2 day fast with neuromuscular electrical stimulation (NMES) exercise would be a practical, acceptable and suitable stimulus.

Sophisticated NMES techniques can now exercise aerobically and train individuals. This has been shown in the comparatively fit⁴, those with cardiac failure, the sedentary⁵ and in the obese (unpublished data). This form of treatment is considered acceptable and even at moderate intensities can elicit a substantial aerobic effect.^{6,7} At

aggressive intensities it has been shown to induce a maximal heart rate while exercising at up to 80% of $\text{VO}_{2\text{max}}$.⁸ Importantly, in this context, we observe that it consistently exercises at much higher respiratory exchange ratio (RER) than voluntary exercise. While controversially some consider that NMES preferentially recruits motor units supplied by larger motor neurons, example type IIb fibres.⁹ A recent study by our research group showed that nine obese subjects (body mass index $41.5 \pm 5.5 \text{ kg/m}^2$) could exercise at about 50% of their $\text{VO}_{2\text{peak}}$ for 1 h. Interestingly, at all electrical stimulation intensities they consistently and overwhelmingly used carbohydrate as the substrate, averaging 85% of total energy expenditure, with fat oxidation accounting for 14%. Percentages derived from metabolic gas analysis (Quark B2, Cosmed, Italy).

It was hypothesised that if one could exercise muscle with NMES while in a fasting state carbohydrate/glycogen reserves could be rapidly depleted. This would be evident in a shift away from carbohydrate oxidation. Exercising in this state may constitute a superstimulus for muscle ordinarily dependent on carbohydrate oxidation for NMES. Other stimuli may be prolonged relative hypoglycaemia, lower free fatty acid levels, ketogenesis, using muscle fibres not generally recruited by this population etc. As has been noted by Chakravarthy exercising in the glycogen depleted state has very different biochemical effects and is likely to affect gene expression differently.¹ Exercising when glycogen levels are low results in greater transcriptional activation of interleukin-6,¹⁰ pyruvate dehydrogenase kinase 4¹¹,¹², hexokinase,¹² and heat shock protein 72.¹³ Furthermore, inhibiting muscle glycogen repletion postexercise resulted in a greater and more sustained elevation of GLUT4 mRNA and protein, compared with when glycogen repletion was allowed to occur by giving a high-carbohydrate diet.¹⁴

In addition to potential biochemical advantages, we chose NMES exercise as it is easily controlled; it can be done with the patient lying in a hospital bed; our experience suggests that obese people may be able to exercise at moderate intensities for longer with NMES than the equivalent voluntary exercise, and lastly, up to half diabetic patients may have physical barriers to conventional exercise¹⁵ and many of these would be able to use the NMES.

It is hoped that this case study may spur others on to consider new approaches to treating type 2 diabetes and the potential advantages of the new NMES techniques. As this is a new technique it was prudent to test it on a healthy volunteer.

INVESTIGATIONS

Methods

A medical doctor with 10 years NMES experience undertook the experiment. He was 40-years-old, non-diabetic, comparatively fit and in good general health. The subject fasted for 44 h (only water allowed) and during which time he repeated the NMES exercise session three times. NMES session was recorded. A baseline-fasting, during and post dual energy E-ray absorptiometry (DXA) scan was taken.

The NMES protocol: the subject donned thigh wraps incorporating four electrodes per leg. Through these a staggered sequence of complex pulses induced rhythmic muscle contractions. The system is designed to comfortably recruit large lower limb muscle bulk – including the glutei and calves. The units were supplied by Bio-Medical Research, Galway, Ireland. A more detailed description of the pulses is described elsewhere⁴ and a full description is available from the authors.

Each session was intended to be of 1 h duration following a set pattern. They were preceded by a 5 min rest to establish resting/baseline values. At 5 min intervals the stimulation intensity was increased by a predetermined amount until, at 40 min, an intensity of 55 units /110 milliamps (mA) was reached. This was kept steady for a further 20 min which was followed by 5 min cool-down.

A non-fasting session was completed a week before for comparison. The fasting began after a large evening meal of mixed substrates. No exercise sessions were undertaken that day. The following day, 20 h into the fast, an exact replica of the exercise session was undertaken. Again after a subsequent 20 h, a final exercise attempt was made at 42 h. This session was paused at 45 min due to extreme fatigue. The subject had a coarse tremor with the stimulation paused. His blood glucose was 3.2 mmol. He elected to continue at a reduced intensity (60 mA) for 40 min.

Metabolic measurement: a breath-by-breath metabolic gas analyser (Quark B2, Cosmed, Italy) was prewarmed and properly calibrated prior to each NMES session. Heart rate was recorded with a precordial strap, (Polar; Finland). Glucose was monitored using standard technique, pin-pricks (OneTouch; LifeScan, Milpitas, California, USA) and

a continuous monitor (Guardian RT; Medtronic Minimed, Northridge, California, USA). Body position was marked on the DXA scanner (Lunar; GE Healthcare, Waukesha, Wisconsin, USA) for accurate repeat positioning and no manipulation was done to the image. The first scan was done after overnight fasting (at 14 h), another the following day (at 38 h) and the post scan was at the end of the fast (at 44 h).

OUTCOME AND FOLLOW-UP

Results

Figure 1 displays the main metabolic results. In a non-fasting state the percentage of energy expenditure from carbohydrate metabolism (CHO%) was around 50% at rest. On fasting, this as you would have expected, dropped to close to zero. In the non-fasting state the NMES CHO% was nearly 100% at all intensity levels. On fasting, this reduced to below 50% and during the last exercise session (at 42 h) dropped to close to zero. The last hour of exercise was completed with a mean blood glucose of 2.8 mmol/l.

Excepting the last exercise session the oxygen consumption (VO₂) and energy expenditure remained remarkably replicable. Rising to 26–28 ml/kg/min, or over 600 Kcal/h.

The resting heart rate was 55–60 for the first three NMES sessions. As the third session (at 40 h) progressed it diverged, exceeding age-predicted maximal heart rate of 180 bpm. For the last 3 min it averaged 196 bpm. Non-fasting and at 20 h it remained in the 160–175 bpm range. By 42 h fasting the resting heart rate, at 75–80 bpm, had not returned to normal. In the postfasting period it remained raised; 3 h post exercise and postprandial it was 94 bpm after 5 min rest. The following morning, on waking, it was 54 bpm (table 1).

DXA results are tabulated. The increase in lean mass is probably due to fluid intake. Unsurprisingly there is a decrease in total body fat, 0.515 kg. The repeat scan reliability of regional fat distribution is not published (to our knowledge) so the apparent preference for android fat loss over gynoid fat loss should be treated with caution; loss of 0.069 kg versus a gain of 0.005 kg.

DISCUSSION

The combination of NMES and fasting seemed to created the desired conditions; a large demand for carbohydrate from the muscles which the system was unable to provide. It compensated for this with a clear shift towards fat oxidation during the sessions. The oxygen consumption levels of the +40 h session was similar to previous sessions however, this seems to have been achieved at the cost of higher heart rate – above age-predicted maximal, perhaps consistent with an enhanced sympathetic drive to increase substrate availability.

The metabolism of muscles not directly exercised was also clearly affected. Two hours after finishing the protocol

Table 1 DXA-scan results

	Total lean (kg)	Total fat (kg)	Android fat (kg)	Gynoid fat (kg)
At 14 h	59.717	10.058	0.832	1.910
At 38 h	59.456	9.693	0.792	1.929
At 44 h	60.500	9.543	0.763	1.915
Gain/loss (kg)	0.783	−0.515	−0.069	+0.005

Figure 1 Percentage carbohydrate of total substrate used, heart rate and oxygen consumption (ml/kg/min) while exercising in the non-fasting state and after 20, 40 and 42 h fasting.

the subject got an arm cramp from holding a phone up to his ear for a few minutes.

The physiological conditions induced by the protocol seem extreme but are probably similar to the ‘famine and activity’ of our ancestors. It is possible then that they could constitute a superstimulus. Beaudet *et al*¹⁵ argue that there are biologically important thresholds for disease. We postulate that with the ready availability of food and comparatively low levels of exercise many rarely or never exercise in the glycogen depleted state. They may thus be deprived of metabolic cycling and hence regulatory controls that would have been

induced in our ancestors, some of which are referred to previously.^{1 10–14}

Caution would be advised when applying it to others, especially the prediabetic or diabetic populations. Controlled relative hypoglycaemia is part of the treatment. (This subject recorded a 1 h average of 2.8 mmol/l on the second day of fasting). Clearly, this must be very carefully monitored for safety and any medication that actively lowers the blood sugar should be stopped—exogenous insulin, insulin secretagogues etc. β -blockers and other common medications would also make the clinician hesitant to try this approach. Any additional cardiovascular risk may

prohibit this treatment. It seems sensible to add in salt, perhaps a little potassium and some micronutrients during the fast. The subject in this study sweated copiously and experienced 'salt hunger' after breaking the fast. The experiment was performed by trained and experienced professionals and should not be repeated at the home place.

The protocol could be improved upon. An accelerated program of, say, 20 h would be desirable. The target population may have lower glycogen reserves than the comparatively fit subject of this study. Walking could be alternated with NMES. Since the two modalities preferentially target different muscle fibres there may be additional benefit. Instead of 1 h NMES sessions a prolonged NMES exercise session lasting 8–10 h may compress the programme. This could follow an overnight fast. In order to mimic the metabolic cycling of our ancestors the putative treatment may need to be undertaken periodically.

The demographics and disease trends show that our present approaches are failing most patients who proceed through prediabetes towards diabetes and a lifelong condition. Anything which may interrupt that progression is worth investigating. This study shows a viable way to mimic the famine plus activity stimulus of our ancestors.

Learning points

- ▶ We are failing most patients who proceed from prediabetes to type 2 diabetes and never regain normal glucose metabolism. New approaches should be sought.
- ▶ The famine-plus-physical activity of our ancestors may constitute a superstimulus to improve glucose metabolism. This hypothesis remains unproven but is credible.
- ▶ A shift away from carbohydrate substrate utilisation during NMES exercise, while fasting, suggests the depletion of carbohydrate reserves.
- ▶ Controlled, supervised NMES exercise in a fasting state may mimic this superstimulus and may be acceptable and safe.
- ▶ More research is needed to assess whether this is a safe, acceptable and beneficial in those with type 2 diabetes or prediabetes.

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Patient consent Not obtained.

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