RESEARCH ARTICLE

Exercise training and metformin, but not exercise training alone, decreases insulin production and increases insulin clearance in adults with prediabetes

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Viskochil R, Malin SK, Blankenship JM, Braun B. Exercise training and metformin, but not exercise training alone, decreases insulin production and increases insulin clearance in adults with prediabetes. J Appl Physiol 123: 243–248, 2017. First published May 4, 2017; doi:10.1152/japplphysiol.00790.2016.—Adding metformin to exercise does not augment the effect of training alone to boost whole body insulin sensitivity and lower circulating insulin concentrations. Although lower insulin concentrations (lower supply) following lifestyle and/or pharmacological interventions are primarily attributed to reductions in insulin secretion that match increases in peripheral insulin sensitivity (lower demand), it is unclear whether exercise and/or metformin exert direct effects on insulin production, extraction, or clearance. Thirty-six middle-aged, obese, sedentary adults with prediabetes were randomized to placebo (P), metformin (M), exercise and placebo (E+P), or exercise and metformin (E+M) for 12 wk. Fasting plasma proinsulin (an indicator of insulin production), C-peptide, insulin, and glucose were collected before and after the intervention. Peripheral insulin sensitivity (euglycemic clamp), hepatic insulin extraction, insulin clearance, body weight, and cardiorespiratory fitness were also measured. Fasting proinsulin was unchanged following P (19.4 ± 10.1 vs. 22.6 ± 15.0 pmol/l), E+P (15.1 ± 7.4 vs. 15.5 ± 7.4 pmol/l), or M (24.8 ± 18.9 vs. 16.7 ± 20.3 pmol/l) but was significantly reduced after E+M (18.6 ± 11.9 vs. 13.9 ± 6.7 pmol/l; P = 0.04). Insulin clearance was significantly greater following M (384.6 ± 19.4 vs. 477.4 ± 49.9; P = 0.03) and E+M (400.1 ± 32.0 vs. 482.9 ± 33.9; P = 0.02) but was unchanged in P or E+P. In this study, metformin combined with exercise training reduced circulating proinsulin, and both groups taking metformin increased insulin clearance. This suggests that adding metformin to exercise may augment or attenuate training effects depending on the outcome or organ system being assessed.

NEW & NOTEWORTHY Exercise is increasingly viewed as medication, creating a need to understand its interactions with other common medications. Research suggests metformin, a widely prescribed diabetes medication, may diminish the benefits of exercise when used in combination. In this study, however, metformin combined with exercise training, but not exercise alone, lowered proinsulin concentrations and increased insulin clearance in adults with pre-diabetes. This may directly influence personalized prescriptions of lifestyle and/or pharmacology to reduce diabetes risk.

insulin secretion; proinsulin; hepatic extraction; insulin clearance

A KEY ASPECT of type 2 diabetes (T2D) prevention is the ability to match appropriately the production and secretion of insulin with the demand of whole body insulin resistance. Up to 70% of individuals with prediabetes (fasting and/or postchallenge glucose concentrations above normal but below the range of frank T2D) are characterized by an inappropriate matching of insulin secretion and sensitivity (7), and without lifestyle or pharmacological intervention the transition from prediabetes to T2D is highly likely (25). Results from the U.S. Diabetes Prevention Program suggest that both lifestyle intervention (comprising weight loss and increased physical activity) and the antihyperglycemia medication metformin delay the transition from prediabetes to T2D (13). Despite a plausible expectation of additivity, recent evidence suggests that combining metformin and exercise training confers no added benefit to whole body insulin sensitivity and markers of cardiovascular risk when compared with exercise training alone (9, 19, 20). Lifestyle interventions such as physical activity typically increase whole body insulin sensitivity, which leads to a compensatory reduction in circulating insulin concentrations (6). Although most of this compensatory response is a result of reduced insulin secretion (13), insulin concentrations may also be influenced by changes in insulin production (i.e., the conversion of proinsulin to insulin and C-peptide) within the β-cells of the pancreas and/or adjustments to insulin extraction and clearance by the liver.

Proinsulin is the precursor prohormone to insulin and C-peptide primarily contained within the β-cells of the pancreas and serves as a biomarker of insulin production. Elevated circulating proinsulin concentrations represent a mismatch between glycemia and the synthesis and release of insulin. It is therefore not surprising that total proinsulin concentrations, as well as the ratios of proinsulin to both insulin and C-peptide, are elevated in adults with prediabetes (15, 30). Additionally, hyperproinsulinemia is associated with both the development and severity of T2D (17, 26) and may serve as a link between impaired glycemic control and cardiovascular disease (4, 31). Circulating proinsulin concentrations are reduced following intervention with lifestyle or metformin (13), but the effects of combining the two interventions are unknown. The removal, extraction, and clearance of insulin after it is produced and released from the β-cell comprise two distinct components, first-pass hepatic insulin extraction (HIE) and insulin clearance (IC). HIE involves the degradation of insulin by the liver after secretion from β-cells but before reaching the general circulation (27). Obese individuals and individuals with hyperinsu-
linemia often display reduced HIE (12, 24), which may partly contribute to their elevated circulating insulin concentrations. HIE may be higher following interventions that reduce hyperinsulinemia or improve glucose tolerance (14), however, it is rarely measured in lifestyle and pharmacological interventions. As a result, little is known about how HIE changes with respect to alterations to insulin secretion and sensitivity. HIE may act as a temporary means by which circulating insulin concentrations can be adjusted to match daily fluctuations to insulin sensitivity without the need for up- or downregulation of insulin production within the β-cell, and HIE is often reduced following short-term (i.e., <2 wk) interventions that induce transient insulin resistance (e.g., overfeeding) and increased following short-term interventions that increase peripheral insulin sensitivity, such as exercise (14, 24). IC, or the systemic breakdown of insulin following release into the general circulation, occurs primarily in the liver (~80%) and kidney (~20%) and is also reduced in obesity (1, 29) and prediabetes (3, 22). IC may respond to pharmacologically augmented weight loss (11), but the effects of lifestyle interventions such as exercise training on IC are unclear.

Insulin production and clearance may lie outside of the closed-loop relationship between whole body insulin sensitivity and compensatory insulin secretion. As a result, changes to these tissue-specific outcomes following lifestyle and/or pharmacological interventions may not be effectively captured with tools (e.g., euglycemic clamp) and metrics [e.g., homeostasis model assessment of insulin resistance (HOMA-IR)] used to evaluate systemic changes to insulin sensitivity and secretion. There is a pressing public health need to maximize the efficacy and precision of T2D prevention, which requires evaluating the independent and interactive effects of lifestyle and pharmacological interventions. Given that exercise training and metformin may regulate glycemic control via different physiological mechanisms of action, their independent and combined effects on insulin production and clearance could impact their utility as agents to prevent or delay diabetes. Thus the purpose of this study was to evaluate the effects of a 12-wk exercise training and/or metformin intervention on insulin production, clearance, and extraction. Given our previous work suggesting that combined metformin and exercise training is not more beneficial than exercise alone with respect to cardiometabolic health (19, 20), we hypothesized that metformin would not confer any added benefit and may even blunt the beneficial effects of exercise training on IC, HIE, and proinsulin processing.

**METHODS**

**Overview.** The protocol has been previously described in detail elsewhere (19, 20). Briefly, overweight to obese sedentary women and men (Table 1) with impaired glucose tolerance, as determined by a 75-g oral glucose tolerance test, were randomly assigned to one of four groups: placebo (P; n = 8), metformin (M; n = 9), exercise training and placebo (E+P; n = 9), and exercise training and metformin (E+M; n = 10). Exclusion criteria were smoking, weight instability (>5-kg change over previous 6 mo), regular physical activity (>60 min/wk), or contraindications to metformin. Peak aerobic capacity (V\textsubscript{O2peak}; cycle ergometer), maximal strength (1-repetition maximum) for key muscle groups), and body composition (dual X-ray absorptiometry, DEXA; Lunar Technologies, Chicago, IL) were tested before and after the intervention. All participants were verbally briefed about the study and signed informed consent documents approved by the University of Massachusetts Amherst Institutional Review Board.

**Intervention protocol.** All participants were instructed to maintain baseline diet and physical activity levels throughout the 12-wk intervention, and no change in diet (3-day diet records) or habitual ambulation (pedometer) was observed (19). Participants were randomly assigned to receive metformin (1,000 mg twice per day separated by 8–12 h) or an identical placebo and further subdivided into exercise training (3 days/wk, 225 total minutes of supervised aerobic and resistance exercise) or nontraining groups. Aerobic exercise consisted of 135 min/wk on a cycle ergometer at a heart rate corresponding to 65% V\textsubscript{O2peak}. Resistance training consisted of two 45-min strength training sessions on nonconsecutive days, which focused on upper- and lower-body major muscle groups (e.g., bench press, leg extension) at a resistance of 60–70% 1-repetition maximum.

**Blood collection and hyperinsulinemic euglycemic clamp.** Following 24 h of dietary and physical activity control (meals to ensure caloric and macronutrient balance) and a 10- to 12-h overnight fast, blood samples were taken from an indwelling catheter placed in an antecubital vein. Blood samples were collected, and plasma was separated in tubes containing EDTA (proinsulin, insulin, and C-peptide) and NaF (glucose) and stored at –80° for subsequent analysis. Following the fasting blood draw, a 120-min hyperinsulinemic euglycemic clamp [5 nmol, 80 milliunits (mU/m)⁻²·min⁻¹] with stable isotope tracers was used to determine peripheral (skeletal muscle) and hepatic insulin sensitivity. Details of the isotope analysis techniques used to calculate rates of glucose disappearance and suppression of endogenous glucose appearance (a metric of hepatic insulin sensitivity) can be found in Malin et al. 2012 (19).

**Biochemical analysis.** Fasting blood glucose was determined using the glucose oxidase method (GM7 analyzer; Analox Instruments, Lunenburg, MA). Fasting plasma proinsulin, insulin, and C-peptide concentrations were determined using a commercial radioimmunoassay (Millipore, Billerica, MA). Whole body insulin sensitivity was measured by the hyperinsulinemic-euglycemic clamp (Euglycemic Clamp System; Quinton Instruments, Seattle, WA), which measures the amount of insulin needed to achieve euglycemia and is expressed as the product of the insulin infusion rate and the resulting plasma insulin concentration, as previously reported by Marini and colleagues (21, 22). Whole body insulin sensitivity was determined by the ratio of plasma proinsulin to plasma C-peptide concentrations. The hyperinsulinemic-euglycemic clamp was used to determine hepatic insulin sensitivity, which was calculated as the product of the insulin infusion rate and the resulting plasma insulin concentration, as previously reported by Marini and colleagues (21, 22). Whole body insulin sensitivity was determined by the ratio of plasma proinsulin to plasma C-peptide concentrations. The hyperinsulinemic-euglycemic clamp was used to determine hepatic insulin sensitivity, which was calculated as the product of the insulin infusion rate and the resulting plasma insulin concentration, as previously reported by Marini and colleagues (21, 22). Whole body insulin sensitivity was determined by the ratio of plasma proinsulin to plasma C-peptide concentrations.
significant changes to first-pass HIE in the control group or any percentage (fasting plasma glucose (Glucose, mmol/l) and change in insulin sensitivity (Insulin sensitivity (Rd/I, mg·kg·FFM−1·pmol−1·ml−1)).

<table>
<thead>
<tr>
<th></th>
<th>P</th>
<th>M</th>
<th>E+P</th>
<th>E+M</th>
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</thead>
<tbody>
<tr>
<td>Glucose, mmol/l</td>
<td>5.34 ± 0.18</td>
<td>5.23 ± 0.24</td>
<td>5.45 ± 0.25</td>
<td>5.86 ± 0.21</td>
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<tr>
<td>Post</td>
<td>5.29 ± 0.12</td>
<td>5.28 ± 0.25</td>
<td>5.41 ± 0.21</td>
<td>5.49 ± 0.13*</td>
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<tr>
<td>Insulin, pmol/l</td>
<td>139.9 ± 28.9</td>
<td>152.9 ± 27.5</td>
<td>94.9 ± 11.5</td>
<td>95.6 ± 20.8</td>
</tr>
<tr>
<td>Post</td>
<td>149.9 ± 34.0</td>
<td>119.7 ± 26.3</td>
<td>84.5 ± 9.7*</td>
<td>80.3 ± 13.9</td>
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<tr>
<td>C-peptide, pmol/l</td>
<td>874.1 ± 151.0</td>
<td>1375.1 ± 142.8</td>
<td>1154.9 ± 195.8</td>
<td>1052.2 ± 96.4</td>
</tr>
<tr>
<td>Post</td>
<td>909.8 ± 142.3</td>
<td>1226.4 ± 150.7</td>
<td>983.2 ± 169.3*</td>
<td>765.8 ± 76.4*</td>
</tr>
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<td>PI/I, pmol</td>
<td>0.15 ± 0.02</td>
<td>0.16 ± 0.03</td>
<td>0.27 ± 0.11</td>
<td>0.24 ± 0.04</td>
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<tr>
<td>PI/C, pmol/pmol</td>
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<td>0.21 ± 0.03</td>
<td>0.19 ± 0.03</td>
<td>0.17 ± 0.03</td>
</tr>
<tr>
<td>Hepatic extraction, %</td>
<td>71.2 ± 3.8</td>
<td>74.4 ± 4.0</td>
<td>84.4 ± 1.7</td>
<td>84.2 ± 3.1</td>
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<tr>
<td>Post</td>
<td>75.8 ± 3.2</td>
<td>79.5 ± 3.2</td>
<td>83.3 ± 2.6</td>
<td>79.8 ± 5.1</td>
</tr>
</tbody>
</table>

Data are presented as means ± SE. R* is rate of glucose disappearance; PI/I, fasting proinsulin-to-insulin ratio; PI/C, fasting proinsulin-to-C-peptide ratio. *Significant change from baseline (P < 0.05).

**Statistics.** Data were analyzed using R statistical software (Vienna, Austria, 2010, http://www.R-project.org). Baseline and group differences were evaluated using a one-way ANOVA. Pre- to postdifferences within groups were determined using paired t-tests. Pearson product moment correlation coefficients were used to determine associations among changes in proinsulin, HIE, and IC as well as changes in insulin action and markers of cardiometabolic health. Statistical significance was accepted as P < 0.05.

**RESULTS**

**Baseline characteristics and effects of training.** Baseline body weight, fitness, insulin sensitivity, and physical activity levels were similar among groups (Table 1). As reported previously (19, 20), VO2peak increased in both E+P (+18%) and E+M (+10%), and weight loss was greater after M (+4%) and E+M (+7%) compared with P (0%) and E+P (−2%). Insulin sensitivity increased following all treatments (Table 2), and the rise in sensitivity was 25–30% greater in E+P compared with E+M (19). Whereas there were no changes to fasting glucose, insulin, or C-peptide in the P and M groups, there were significant reductions in fasting plasma insulin and C-peptide following E+P and significant decreases in fasting plasma glucose and C-peptide in the E+M group (Table 2).

**Proinsulin and proinsulin ratios.** Baseline proinsulin concentrations did not differ among groups. Compared with baseline, fasting plasma proinsulin was not different in P, M, or E+P, however, proinsulin concentrations were significantly lower following E+M (Fig. 1). There were no significant differences in the proinsulin-to-insulin or proinsulin-to-C-peptide ratios across the interventions (Table 2). There was also no significant correlation among the change in fasting proinsulin and change in insulin sensitivity (r = −0.127, P = 0.46), fasting plasma glucose (r = 0.199, P = 0.25), or body fat percentage (r = 0.323, P = 0.64).

**Hepatic extraction and insulin clearance.** There were no significant changes to first-pass HIE in the control group or any of the intervention groups (Table 2). There was also no significant correlation between the change in HIE and the change in fasting proinsulin (r = 0.053, P = 0.76), insulin sensitivity (r = −0.064, P = 0.96), body fat percentage (r = 0.139, P = 0.88), or body weight (r = −0.208, P = 0.43). Steady-state plasma insulin was significantly lower in M and E+M, but there was no difference in P or E+P (Fig. 2A). Similarly, insulin clearance was also significantly increased in M and E+M and unchanged in P and E+P (Fig. 2B). Postintervention insulin clearance was also significantly greater than insulin clearance in the placebo group, both before and following completion of the intervention period (Fig. 2B). There was a significant association between the change in insulin clearance and defined as the glucose disposal rate during the last 30 min of the clamp divided by the steady-state plasma insulin concentration.

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and change in whole body insulin sensitivity ($r = 0.344$, $P = 0.014$), however, there was no association between insulin clearance and fitness ($r = 0.291$, $P = 0.15$), body fat ($r = -0.143$, $P = 0.42$), or hepatic insulin sensitivity ($r = 0.081$, $P = 0.78$).

**DISCUSSION**

In this study, fasting proinsulin was significantly reduced ($-24\%$) only after exercise training was combined with metformin. There was a 20% decrease with metformin alone that was comparable with the combined intervention, but this was not statistically significant. Additionally, rates of steady-state insulin clearance during a hyperinsulinemic euglycemic clamp were also significantly greater following 12 wk of metformin with or without exercise training but not with placebo or exercise training alone. These results surprised us because we expected both proinsulin concentrations and insulin clearance to follow a similar pattern to that of insulin sensitivity, which was most strongly enhanced by exercise training alone (19, 20). Consistent with findings from our previous studies, these changes to proinsulin and insulin clearance were not influenced by age or sex differences. The decoupling of changes to proinsulin and insulin clearance from changes to insulin sensitivity and fasting insulin suggests that metformin and exercise differentially impact the relationship between insulin demand (tissue sensitivity) and supply (production and secretion).

There are several explanations for these results. In the current study, only the two groups that received metformin lost weight. Weight loss drives many of the beneficial outcomes of lifestyle or pharmacological interventions on cardiometabolic health/disease risk, and this may be true for insulin clearance as well. However, the driving force behind these positive changes is generally considered to be loss of fat, particularly loss of abdominal fat (19). In our study, it was only the two exercise groups, not the metformin-only group, who lost total and central adiposity, and a causal relationship between weight/fat loss and both lower proinsulin and greater insulin clearance is not supported. Similarly, although greater whole body insulin sensitivity was strongly associated with higher cardiorespiratory fitness (CRF), there was no change to fasting proinsulin or insulin clearance in the exercise-only group, which showed the largest rise in CRF. In contrast, metformin alone caused a 20% reduction in proinsulin and a 20% increase in insulin clearance despite no change in CRF. These results suggest that changes in CRF are not necessary to alter fasting proinsulin or insulin clearance.

It is also possible that in men and women with prediabetes, elevated fasting proinsulin levels and increased insulin clearance more closely reflect fasting hyperglycemia than hepatic or peripheral insulin resistance. If so, fasting proinsulin may only decline subsequent to, or concomitantly with, lowering of fasting glucose concentrations. We observed no association between change in proinsulin and changes in fasting glucose. However, it is conceivable that any relationship between the two was obscured by the relatively modest fasting hyperglycemia at baseline, restricting the magnitude of any declines in fasting glycemia and, therefore, proinsulin. The only group that exhibited a statistically significant decline in proinsulin was the E+M group, which also had a statistically significant reduction in fasting glucose concentration. Additionally, whereas there were significant reductions in proinsulin (E+M) and increases in insulin clearance (M, E+M) over the intervention period, there were no significant differences in proinsulin or insulin clearance between groups at baseline or after each intervention. It is unclear why these within-group changes did not manifest as significant differences between groups following the intervention period; however, the high degree of variability within groups, especially the metformin-only group, may have played a role.

In addition to suppressing hepatic gluconeogenesis (18), metformin may also affect signaling pathways within the β-cell (16), and it is possible that metformin, but not exercise, has a direct impact on insulin production in humans but exercise does not. Although only exercise training and metformin significantly lowered proinsulin concentrations, the pattern of changes in the metformin groups suggests that metformin may act directly on the β-cell to lower insulin production. This hypothesis is clearly preliminary but is supported by recent work in isolated pancreatic β-cells in which metformin altered
intracellular insulin processing via an AMP kinase-related mechanism (10, 23). It is also possible that metformin directly influences hepatic and renal insulin clearance via upregulation of key insulin degrading enzymes and functions (2, 8) but that exercise training has a minimal effect on this degradation process. Directly testing how the combination of exercise training and metformin impacts insulin synthesis within the β-cells of the pancreas, as well as insulin degradation within hepatocytes, will require animal models and cell culture work in follow-up studies.

In contrast to the effects of metformin, discord among changes in circulating insulin, proinsulin, insulin sensitivity, and insulin clearance in the exercise groups suggests that exercise training may modify glycemic control primarily by enhancing peripheral insulin sensitivity and consequently reducing insulin secretion. In addition to a lack of effect of exercise training alone on fasting proinsulin concentrations, we observed no effect of exercise training alone on either measure of insulin clearance (HIE or IC). However, the calculation of hepatic insulin extraction using fasting C-peptide and insulin kinetics relies on several assumptions (5), and without a pre- and postintervention glucose challenge it is hard to argue that hepatic extraction has no role in the adaptations to glycemic control following exercise training. The lack of a pre- and postintervention intravenous or oral glucose challenge also limits the scope of insulin secretion to fasting C-peptide and insulin alone, and therefore the potential relationship between changes to insulin secretion and insulin production/clearance following exercise training and/or metformin is incomplete. A complete understanding of how exercise training or metformin alters insulin supply and demand will require cleverly designed studies to tease apart several interrelated processes.

Understanding the effects of exercise or metformin on measures of glycemic control requires considering the larger context. The hyperbolic law of insulin kinetics suggests that the relationship between insulin demand (sensitivity or resistance) and supply (secretion and clearance) is coupled, such that decreasing sensitivity leads to higher circulating insulin concentrations and vice versa (28). The current study suggests that metformin, but not exercise alone, could change insulin production and clearance without the necessity for upstream changes to insulin sensitivity. If true, there are potentially important clinical ramifications. For example, one of the oft-cited benefits to improving insulin sensitivity is reducing hyperinsulinemia and “resting” the pancreas to preserve β-cell function. If lower circulating insulin is a result of changes in postsecretion insulin clearance instead of reductions in first- and/or second-phase insulin secretion, there may be little or no reduction in β-cell “stress.” Additionally, if there is recognized value in reducing insulin secretion by the islets regardless of the degree of insulin reaching the general circulation, there may be practical reasons to choose between metformin or exercise for patients who are still able to compensate for insulin resistance with hyperinsulinemia. The divergent impact of exercise and/or metformin on tissue-specific (e.g., proinsulin and insulin clearance) compared with whole body (e.g., insulin action) metrics of glycemic control suggests that the utility of selecting one treatment vs. the other or combining both treatments is outcome-specific. Scaling up to the critical public health issue of preventing diabetes and cardiovascular disease in humans, the independent and combined actions of physical activity and/or metformin on the transition from prediabetes to T2D is difficult to predict from studies of insulin sensitivity or biomarkers. To understand the comparative efficacy of physical activity and/or metformin on T2D prevention, studies will need to be conducted in the target population with the development of frank T2D as the primary outcome.

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GRANTS

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS


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