1st International Congress on Cancer Prevention
ICCP 2024
Zanjan, Iran
18-19 September 2024
University of Zanjan

3-month physical activity and fat mass loss regulate breast cancer-related inflammatory markers in obese and overweight postmenopausal women

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Abstract

Chronic low-grade inflammation plays a role in the pathogenesis of several chronic diseases including cancer. exercise training have been supposed to modulate inflammatory markers.

The effects of a concurrent training on gene expression TGF-β1 was evaluated in an unblinded randomized controlled clinical trial .Thirty participants [healthy postmenopausal women with high breast density, age 45–55years, BMI >25 kg/m2, inactive and had an elevated Gail 5-year risk score of breast cancer (>1.66%)] were randomized to two arms: training group (TG, n=15) and control group (CG, n=15). Participants took part in a 12-week supervised intervention, 5 days/week training and 60 min/session. Before and after the intervention, body composition was assessed, and blood samples were obtained to evaluate estradiol, TGF-β1.

In response to training, a reduction in total fat mass was found (5.3%; $P<0.05$), while an increase in lean body mass was observed in the TG group (1.5%; $P<0.05$). The expression of the TGF-β1 gene decreased, but this change was not statistically significant ($P>0.05$).

The exercise training and in fact, exercise-induced fat mass loss seem to modify the pro inflammatory markers in postmenopausal women that is an established risk factor of breast cancer. Thus, this study provides additional evidences to the intricate interaction among cytokines, adipose tissue, and muscle mass in postmenopausal women.

Keywords: Body composition, Breast cancer prevention. concurrent Training. Transforming growth factor-beta 1. Menopause

1- Introduction

Breast cancer (BC) is the most common malignancy worldwide and 2.3 million new cases were recorded representing 11.7 % of all the total cases of cancer. Also, a significant increase in the mortality rate for BC patients has been observed [1,2]. Multiple steps of carcinogenesis have been observed to be involved in BC and its progression [2,3].

It is widely accepted that chronic low-grade inflammation may play a role in breast cancer [1]. A higher level of inflammation, associated to the decline in circulating estrogens, has been documented among postmenopausal women. Also obesity and abdominal adiposity have been associated with a pro inflammatory profile [2].

Transforming growth factor-beta (TGF-β) is a dynamic growth factor that regulates diverse cellular functions and is a key regulator involved in both normal mammary gland development and cancer progression and metastasis [4]. It plays a dual role, in mammary carcinogenesis, and during the early stage of the tumor, it acts as a tumor suppressor via its anti-proliferative functions. During later stages of tumor development, it acts as a tumor promoter [5] which is known as the TGF-β switch. However, a meta-analysis that was carried out to find the association of TGF-β polymorphism with BC risk, showed TGF-β1 29T > C polymorphism a link with a greater risk of BC in the Asian population, and the same polymorphism in the Middle Eastern population favored lower probabilities of BC [6]. The most widely studied component of the TGF-β pathway in breast cancer is TGF-β type I. It binds with a high affinity to TGF-β type II receptor (TGF-β-RII), which trans activates TGF-β type I receptor to initiate an intracellular signaling cascade by bringing about phosphorylation of 2 receptor-regulated Smads (Smad2 and 3), recruiting the common-partner Smad (Smad 4) to form the Smad4-Smad2/3 complexes, and translocating to the nucleus as the transcription factor to regulate expression of target genes [7,5]. Thus far, the clinical prognostic role of TGF-β pathway components in human breast cancer remains elusive, which may be due to the complexity introduced by a variety of other molecules and systemic factors, such as estrogen receptor α and human epidermal growth factor receptor 2 status, common-partner and inhibitory Smads, early-age onset, and menopausal status [7].

Studies indicate that the TGF-β superfamily also has pleiotropic roles in metabolism, energy homeostasis, and adipogenesis, mainly through downstream molecules of Smads that induce obesity and other metabolic abnormalities [8]. In human subjects, a significant association between BMI and TGF-β1 concentration in circulating blood [1,8] or adipose tissue [9] has been reported. Because of the intrinsic gene-environment interaction between TGF-β1 and obesity, modulation of the TGF-β1 pathway has been suggested as a promising treatment strategy for obesity and its comorbid conditions [7].

In addition to BMI, physical activity appears to be another systemic factor associated with the TGF-β1 signaling pathway. Studies reveal that physical exercise significantly increases the serum level of TGF-β1 in human subjects [10]. Based on current knowledge of the multifaceted roles of the TGF-β1 pathway in cancer and systemic metabolism, it is

plausible that the TGF-β1 pathway may be associated with BC outcome, and this association may be affected by patient characteristics such as BMI and physical activity. Exercise training seem to be a preventing mechanism of in cancer [10,11]. It is suggested that endurance training will raise the antioxidant capacity of skeletal muscles, thereby keeping the muscle mass. Exercise can lower fat percentage, reduce obesity, and decrease low-grade systemic inflammation, which all play a role in cancer pathogenesis. Thus, exercise training is even likely to prevent cancer [11].

Till now various preclinical studies have shed light on the TGF-β1 pathway mechanisms and its context-dependent downstream activity [6–9]. It also showed promising results as exhibiting its candidature as a biomarker for the prediction of BC prognosis as well as targeting its utility as a biomarker may help for the prevention of BC [10]. There is a gap in the literature on the relationship of TGF-β1 expression with adaptation induced by exercise in obese postmenopausal women. This article gives insights into the effect of exercise training (concurrent training: resistance and aerobic exercises) role on TGF-β1 in BC prevention, exploring its status as a potential biomarker that may aid in the prevention of BC and the loopholes in the knowledge that still exists.

2- Methodology

A randomized controlled trial that included concurrent training and a control group in postmenopausal women was conducted. All experimental procedures were approved by the Ethics Committee of the University of Tabriz (IR.TABRIZU.REC.1400.048). Participants provided written informed consent prior participation. They were randomized and stratified to the control group (n=15), training group (n=15) according to a computerized random number generator (1998-2017 RANDOM.ORG).

Initially, 110 participants were recruited from the Department of oncology, after drop-outs, a total of 30 participants took part in the study. Oncologist display study materials to women. Furthermore, posters with information about the study were distributed at the hospital and women who indicated an interest in the study to their medical doctor were contacted by phone. Eligibility was checked during study of medical records and screening visit to hospital women's were included in the study that were postmenopausal (>12 month since last menstrual cycle), age 45-55 years, overweight or obese (BMI>25 kg/m^2), inactive (≤ 150 min / week) and had an elevated Gail 5-year risk score BC(1.66) [12], maximum E2≤66 pg / ml and mammograms were selected at least once in medical centers. Examining the biochemical tests on file, diabetics (FBS≥126mg/dl)[13], participant with hypertension and cardiovascular disease, women with other cancers, individuals who have had major surgery in the past year have been taking hormone or estradiol stimulants (Metformin, ampicillin and hormone replacement therapy)[14]. Additionally, women were excluded if they were regular smoking or drinking alcohol, and if they currently or were planning to participate in a diet program.

This trial involved two control and training groups, the TG group underwent a 12-week intervention. Participants attended three sessions for technique training before starting. The training group (TG, N=13) exercised, while the control group (CG, N=12) did not. The program included five weekly sessions: three endurance (treadmill, stationary bike,

elliptical) and two resistance exercises (eight types, such as knee flexion and chest press), with three sets of 8–12 repetitions at 45-80% of one-repetition maximum and 60-90 seconds rest. Endurance training lasted 60 minutes, with moderate intensity set at 45-85% of heart rate reserve. Fitness assessments were conducted every three weeks, adjusting resistance by 5-10% when participants were ready"Tab. 1".

Table 1: concurrent training protocols

weeks	Endurance exercise			Resistance exercise			
	session	Time (min)	Intensity (HRmax)	session	Time (min)	Intensity (%1RM)	volume
0	3	45	40- 45	2	20-30	40	2×8(60s)
1-2	3	45	55	2	40-50	50-55	2 ×12-15(90s)
3-4	3	48	65	2	60	55-60	3×10-12(90-120s)
5-6	3	51	70	2	60	60-65	3×8-10(90-120s)
7-8	3	54	75	2	60	70	3×8-10(90-120s)
9-10	3	57	85	2	60	70-75	3×8-10(90-120s)
11-12	3	60	85	2	60	75-80	3×8-10(90-120s)

HRmax: maximal heart rate, RM: maximum repetition, Volume: sets x repetitions (inter-set rest)

Women arrived at the lab in a fasted state (8–12 h) for blood draws, body composition assessment, blood pressure (Omron M6 Comfort IT), and fitness evaluations. They performed a submaximal treadmill cardiorespiratory test to estimate VO_2peak using ACSM equations, followed by a VO_2peak test on a bicycle ergometer with pulmonary gas exchange monitored via a breath-by-breath analyzer (Quark CPET). The fat oxidation test started with 5 min of rest, then 5 min at 50 W, increasing by 20 W every three minutes until RER reached 1.0. The VO_2peak test began at 50 W, increasing by 20 W per minute until exhaustion, confirming VO_2peak with at least two of three criteria (RER >1.15, VO_2/HR plateau, or inability to maintain>60 rpm)[15]. Maximal strength was evaluated through a progressive 1RM protocol[16]. Participants filled out health, dietary (3-day records), and physical activity (IPAQ) questionnaires[17]. Body composition was assessed using bioimpedance (X-Scan Plus 950), and waist/hip ratio was calculated from waist and pelvic circumferences[18].

Blood samples were collected and stored at –80 ºC. RNA was extracted with an RNeasy Mini Kit, and 1 µg was converted to cDNA using a Transcriptor kit. qPCR was performed using SYBR Green Master Mix with HGS and GAPDH primers, calculating relative expression via the $2^{-\Delta\Delta Ct}$ method. cDNA synthesis followed Qiagen guidelines, and PCR was conducted on a Stepone plus with a 20 µl final volume: 30 sec at 95 °C, 40 cycles of 5 sec at 95 °C and 30 sec at 60 °C, verified by melting curve analysis. Primers were designed using Runner Gene Primer Software"Tab. 2". [19].

Table 2: Primer specification for cDNA synthesis

Genes	Forward sequence	Reverse sequence
GAPDH	CTTTGGTATCGTGGAAGGAC	GCAGGGATGATGTTCTGG

TGF-β1	TGGAGTTGGACGGCAGTG	TGGAGTTTGTTATCTTTGCTGTCAC

Statistical analysis

Sample size estimation was based on previous studies showing pro-inflammatory cytokine changes post a 12-week exercise intervention. To detect an effect size of 0.45 (α=0.05; 1−β=0.80), 30 postmenopausal women were recruited. Data analysis was conducted using SPSS (v. 25.0) with Shapiro–Wilk test for distribution and logarithmic transformations ($P \leq 0.05$). One-way ANOVA and Chi-squared tests compared baseline groups. A sensitivity analysis included participants attending at least 80% of sessions. Tukey's post hoc test assessed significant differences, with effect sizes noted as eta-squared ($\eta 2$) and Hedges' g (g). Results are presented as mean and 95% confidence intervals (95% CI) with significance at $P \leq 0.05$.

3- Results

Thirty women were enrolled in this randomized-controlled trial. Full 12-week data were available for 25 women with a final sample size of 13 in the training group and 12 in the control group. Two women dropped out of the study due to surgery, urinary incontinence, hyperthyroidism diagnosis and diet program initiation reasons. No harmful adverse events were reported during the trial. Participants' characteristics are presented in Tab. 3. No statistically significant differences were found at baseline among treatment arm.

Table 3: Baseline characteristics of participants assigned to training group (N=13) and control group (N=12).

Variables		**TG (n=13)**	**CG (n=12)**	**P**
Age (years)		52.8±3.8	53.66±3.9	0.79
Age at menopause (years)		50±1.5	49.5±2.4	0.61
Percentage of risk based on Gail model		2.75±0.46	2.05±0.13	0.128
Married status	Married; N%	10(76%)	9(75%)	0.74
	Single; N%	2(15.3%)	2(16%)	
	Widow; N%	1(7.6%)	1(8.3%)	
Education	first grade; N%	7(53.8%)	4(33.6%)	0.1
	College/trade; N%	3(23.33%)	6(50%)	
	University graduate; N%	3(23.33%)	2(8.33%)	
First period	7-11	9(69.2%)	8(66.66%)	0.23
	12-13	4(30.7%)	2(16.66%)	
	≥13	0	2(16.66%)	
First live birth		27.71	28.2	0.96
History of abortion		1.38	0.69	0.6
First-degree relatives with breast cancer; N%		11(84.6%)	10(83.3%)	0.56
History of smoking; N%		0	0	-
History of alcohol consumption; N%		0	0	-
Estradiol(pg/ml)		11.897±3.7	11.83±3.9	0.469
VO_2peak (ml/kg/min)		21.63±1.9	21.32±3.3	0.87
Total physical activity (MET/ min/week)		3970±872	3727±106	0.89

Total calories (Kcal/day)	1883±405	1803±310	0.39
RER	0.82±0.02	0.83±0.02	0.82

Data are mean ± standard deviation or N (%) unless otherwise specified.

Exercise adherence

Participants in the training group attended an average of 90 % (54 sessions of 60) of the exercise sessions [171.5(150,195) minutes of exercise/week].

Maximal muscle strength and cardiorespiratory fitness tests

A statistically significant difference between groups was found in maximal muscle strength (p interaction<0.001; leg press, η^2=0.975; bench press, η^2=0.905) training group significantly increased their leg press 1RM [P<0.001, g=2.730] and bench press 1RM [P<0.001, g=0.879]. According to the submaximal cardiorespiratory fitness test, VO_2peak and RER were not different between groups (p = 0.52 ;p = 0.29, respectively), we observed a pre- and post-intervention increase of peak power output and estimated VO_2peak by 18% and 12% in the concurrent group (P<0.001, g=1.140 and 1.023, respectively).

Changes in body composition

Changes in body composition after the 12-week intervention are shown in Fig. 1. Body weight, fat mass (kg), WHR and BMI were significantly decreased in training group (-1.8%, -7.73%, -1.3%, -3.87% respectively), compare to control group (+0.16%, +1.3%, +0.51% and -0.32% respectively). In lean body mass (kg), no between-group differences were detected, but the pre- and post-intervention comparison revealed a statistically significant increase in the training group (2.5%; P<0.05, g=0.207).

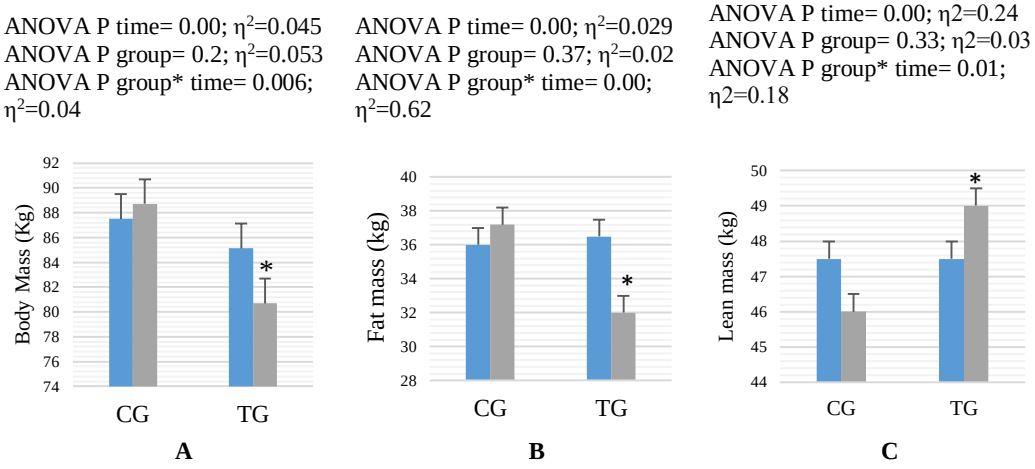
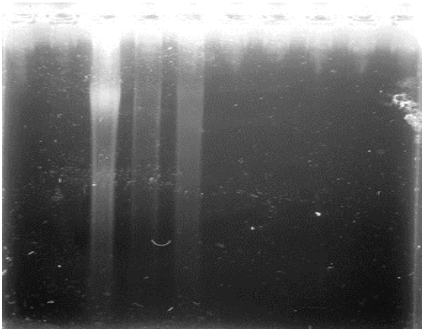


Figure 1: Changes in a) body mass, b) fat mass, c) lean mass, after 12 weeks of intervention. P value [time, group, and time*group (interaction)] of two-way ANOVA analysis. *P 0.05 Compared with baseline. TG training group, CG control group.

The effect of concurrent training on TGF-β1 gene expression in PBMC (peripheral blood mononuclear cell)

One-way ANOVA results indicated no significant difference in TGF-β1 gene expression between the TG and CG groups (F=0.063, P=0.97), although TGF-β1 expression was lower in the PBMC of the TG group. See "Fig. 2."



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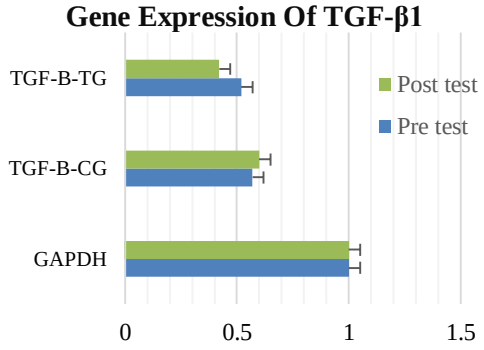

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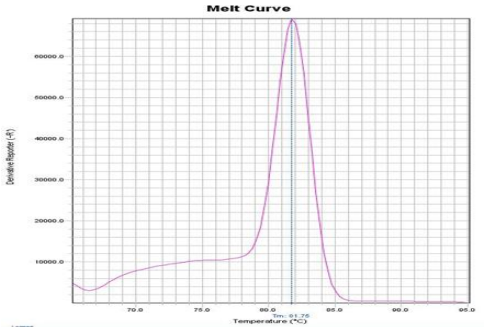

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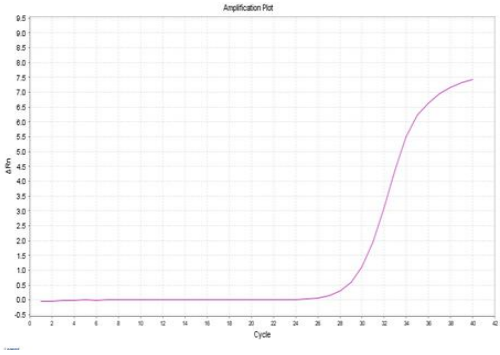

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Figure 2: Alteration of TGF-β1 gene expression in PBMC of postmenopausal women at risk of breast cancer, a) Agarose gel electrophoresis of the PCR product corresponding to the candidate reference gene(GAPDH), b)The effect of concurrent training on TGF-β1 gene expression values were normalized to GAPDH, c) Melt curves from qPCR of TGF-β1 gene, d) Amplification curve generated during the run is measured in real time. Data are mean (SD)*P < 0.05 compared to control, #P < 0.05 compared to pre- intervention, P < 0.05 compared to post. CG: control; TG: training group. Values are relative to GAPDH as an internal control.

4- Conclusions

This randomized-controlled trial investigated the effects of concurrent training on TGF-β1 expression, body composition markers in obese and overweight postmenopausal women. After 12 weeks of training, training groups lost total fat mass; however, a significant increase in lean mass was found in the training group. Moreover, concurrent training stimulate response on TGF-β1 expression, reporting a decrease after concurrent training, but the decrease was not statistically significant.

TGF-β1 levels in the training group were lower than in the control group, but not significantly different. TGF-β1, one of three beta TGF isoforms, influences various cellular functions, including extracellular matrix production. Its gene expression is associated with physical activity. Czarkowska Paczek et al. reported that serum TGF-β1 surged after exercise, increasing from 20.58 ng/ml to 55.37 ng/ml immediately post-workout and to 40.03 ng/ml two hours later[7]. Another study noted an increase in plasma TGF-β1 from 992 pg/ml to 1301 pg/ml after one hour of running at a 3% incline[2].

Pre- and post-diagnostic obesity are known to inversely affect BC prognosis, but whether the body weight of patients has an effect on the prognostic role of the TGF-β pathway is unclear[3]. TGF-β1, a cytokine linked to obesity and aging, is elevated in ob/ob mice, HFD-fed mice, and obese humans. In a study of 9,142 Japanese subjects found a positive correlation between serum TGF-β1 and factors such as age, lifestyle, and BMI, with higher levels in individuals with a BMI > 25 kg/m²[8]. Additionally, Scaglione et al. reported a moderate correlation ($r = 0.52$, $p = 0.0001$) between BMI and TGF-β1 in 58 hypertensive patients[9].

TGF-β has complex pro- and anti-inflammatory roles in various tissues. Rao et al. found that meteorin-like 1 (Metrnl), released during exercise and low temperatures, boosts Ucp1 mRNA and anti-inflammatory genes Il-10 and TGF-β in brown adipose tissue (BAT) [11]. In contrast, Yadav et al. reported that TGF-β1 injection lowered UCP1 in lean mice. Our study showed reduced TGF-β1 mRNA in the PBMCs of obese women, possibly explaining the decreased Ucp1 observed by Rao et al[11]. Although TGF-β1 may have an anti-inflammatory role in BAT, more research is needed to clarify its dual effects.

Brown adiposity tissue can help alleviate health issues related to obesity by regulating the JAK-STAT, TGF-β, and insulin signaling pathways. In exercise-regulated BAT involved in inflammatory responses, the JAK-STAT downstream gene SOC-3 may contribute to leptin resistance. Through exercise, TGF-β1 is activated and upregulated by inflammatory mediators and reactive oxygen species (ROS), thereby regulating the involvement of inflammatory cells such as IL and NF-κB in immune responses. Additionally, saturated fatty acids can activate NF-κB in macrophages, aiding in obesity relief[12]. Experimental studies have demonstrated that an 8-week swimming intervention significantly reduces inflammatory factors and responses in obese mice[13].

It has been demonstrated that TGF-β1 levels are correlated the with BMI, fat mass, and VO_2peak in humans. In addition, high TGF-β1 levels were associated with atypical metabolic profile [14]. In this study, we detected a reduced VO_2peak and RER in postmenopausal women with higher TGF-β1 levels. The reduction in the RER of the participant indicates that this group could use more fat as an energy source [11] or develops an energy expenditure dysfunction. Previous research has shown that to evaluate the energy expenditure, monitored the UCP1 in the brown adipose tissue It is a good criterion.

Excercise training increases energy demand, leading to heightened aerobic and anaerobic metabolism, which in turn raises reactive oxygen species (ROS) production. At low levels, ROS act as signaling messengers, but elevated levels can cause oxidative damage, inhibit proteins, and potentially lead to cell death. While excessive ROS can induce damage, they also stimulate antioxidant defenses[20].TGF-β1 enhances

mitochondrial ROS production in various cells by activating NADPH oxidase and reducing antioxidant enzyme activity, resulting in redox imbalance. Conversely, such imbalance can activate latent TGF-β1 and increase its gene expression, enhancing TGF-β1 activity.Regular exercise prompts adaptations mainly through increased activity of antioxidant enzymes like superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPX), which help mitigate the effects of ROS. Reduced ROS levels limit TGF-β1 activation, leading to lower serum/plasma TGF-β1. Exercise adaptations result in metabolic alterations, neuromuscular recruitment changes, and tissue remodeling, influenced by exercise model, intensity, and volume[20,21].

Controlling TGF-β1 signaling may help prevent cancer and inflammation. We employed chronic exercise, a non-invasive method, to prevent BC. Kim et al found that 24 days of swimming lowered TGF-β1 in aged obese rats[7]. Böhm et al. reported that eight weeks of training reduced TGF-β in the skeletal muscle of middle-aged individuals, linking it to mitochondrial function and insulin sensitivity. Luo et al. and Touvra et al. also observed similar results[13]. Our study confirmed that moderate chronic exercise decreased TGF-β1 in obese women, Interestingly, these data were accompanied by a reduction of body weight.

This study demonstrates that integrating moderate-to-vigorous resistance training with aerobic exercise reduces systemic inflammation in obese postmenopausal women at risk for breast cancer, as reflected by cytokine profiles. Concurrent training enhances performance and may assist in body fat reduction, potentially regulating inflammation and improving quality of life. Although further research is necessary to explore the long-term effects on breast cancer prognosis, the short-term enhancements in physiological biomarkers are encouraging.

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