PRE-WORKOUT SUPPLEMENTATION— THE GOOD, THE BAD, AND THE UGLY

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Approximately half of the United States adult population consumes some form of dietary supplementation, with that proportion rising in physically active adults and athletes (23). One of the most commonly consumed supplements is a "pre-workout." Pre-workouts can be categorized as any supplement ingested prior to an exercise session or sporting event with the intent of increasing mental focus, endurance, blood flow, strength, power, aerobic and anaerobic capacity, or overall perceived increase in energy level.

Pre-workouts come in a variety of forms ranging from single- (e.g., caffeine) to multi-ingredients (MIPS); stimulant versus stimulant-free; and powdered, pill, or liquid form (e.g., energy drinks). While countless formulas exist, Table 1 highlights and breaks down the individual ingredients most often found in these products and how each has been demonstrated to affect the body. Despite conflicting evidence of effectiveness, pre-workouts continue to gain popularity in both recreational and athletic populations due to the anecdotal claims of increased performance, reduced recovery time, and increased perceived energy. However, along with the increased usage of these products, there is an ever-growing cause for concern pertaining to not only their effectiveness, but also safety. Therefore, this article will discuss the most common individual ingredients typically found within pre-workouts and describe *"the good, the bad, and the ugly"* associated with its usage.

NOTE: While this article provides a deeper understanding of the benefits and drawbacks of pre-workout supplementation, the authors do not endorse or condone its use and recommend consulting a physician prior to consuming any dietary supplement.

THE "GOOD"

Despite the manufacturers' claims, research continues to demonstrate inconsistencies on the efficacy of pre-workout supplementation. Overall, the consensus on pre-workout supplementation indicates a trivial-to-small benefit for exercise performance (11,13,15). However, the following advantages, if any, are subject to scrutiny, as large individual responses to pre-workout consumption exist and depend on the mere presence and appropriate dosages of specific compounds within the dietary supplement.

PRE-WORKOUT COMPOUNDS

One such compound, caffeine, is one of the most common ingredients within pre-workouts. Caffeine, alone, has been shown to increase aerobic endurance by up to 15.9% in time-to-fatigue trials, increase muscular strength by ~2 to 7%, and increase mean and peak anaerobic power by ~7 to 8.5% when ingested ~60 min before an exercise session with an average dosage of 5±2 mg/kg of bodyweight (10,11,28,30). However, when caffeine is added to a MIPS, benefits often diminish as proper dosages may be reduced and thus not adequate to produce an ergogenic effect. The recommended dosages for acquiring ergogenic effects from caffeine are 3 – 6 mg/kg of bodyweight (11); yet, many pre-workout supplements contain less than 200 mg of caffeine. Therefore, individuals greater than 150 lb (68 kg) may not experience increases in sport performance, attributed to caffeine, after an MIPS consumption with less than 200 mg of caffeine. Additionally, the consensus shows that doses of caffeine <2 mg/kg of bodyweight do not appear to provide an ergogenic effect; while, doses >6 – 9 mg/kg can cause negative side effects, along with potential decreases in performance (11).

Other common ingredients within a MIPS include creatine monohydrate, citrulline malate, tyrosine, sodium bicarbonate, and beta-alanine, with each compound serving a particular function. For example, creatine monohydrate, a compound derived from three amino acids, assists the creatine phosphate metabolic system to derive a greater supply of potential energy production (i.e., adenosine triphosphate [ATP]). While varying derivatives of creatine exist, creatine monohydrate has been shown to increase skeletal muscle creatine stores by ~20%, enhance muscle recovery, reduce skeletal muscle damage, increase mean and peak power and anaerobic capacity, and promote glycogen restoration (18). Despite the majority of ergogenic benefits for anaerobic activities, the research consensus has shown no consistent benefits of creatine supplementation within aerobic-based or agility-based events (21).

Additional compounds, such as sodium bicarbonate, sodium citrate, and beta-alanine, are often included within a MIPS for purposes of promoting acid-base regulation. Findings have indicated that acidic pH buffers (e.g., beta-alanine) may counteract metabolic acidosis and delay an earlier onset of muscular fatigue (13). For example, competitive rowers found a slightly greater benefit (i.e., ~6 s during a 2,000-meter time-trial) following the chronic supplementation of beta-alanine combined with an acute consumption of sodium bicarbonate compared to chronic beta-alanine intake alone (13). While the combination of compounds may provide an increased benefit to the user, research is still limited pertaining to training outcomes, such as anaerobic power, muscular strength, endurance, and hypertrophy.

PERFORMANCE OUTCOMES

Regarding anaerobic power, pre-workout supplementation, as a whole, has provided little-to-no benefit across various modalities (i.e., treadmill, non-motorized treadmill, and cycle ergometer) (14,20). For example, a MIPS containing a proprietary blend of creatine, branched chain amino acids (BCAAs), taurine, caffeine, B-vitamins, and others, demonstrated only small changes in anaerobic mean (~34 W) and peak (~60 W) power, as well as

a trivial difference in fatigue index (~0.03%) in recreationally-trained males during a Wingate test (20). Furthermore, pre-workout supplementation showed no benefits for jump height, mean and peak power, and fatigue index when consumed prior to a 25-second "all-out" sprint and countermovement jump in collegiate football players despite subjective reports of less fatigue and increased alertness (14). The MIPS consisted of a mixture of various compounds, such as creatine, β-alanine, taurine, n-acetyl cysteine, citrulline malate, beet root extract, BCAAs, tyrosine, and caffeine. It was concluded that the dosages of the individual ingredients within the supplement could not be identified; thus, the overall interpretation of MIPS consumption on anaerobic power is limited.

Pre-workouts are generally consumed prior to resistance-training sessions for increasing muscular strength and endurance, whether through single efforts (i.e., one-repetition maximum [1RM]) or repetitions-to-fatigue for a higher volume-load. While anecdotal accounts suggest greater performance, the literature ranges in conclusions from decreases in performance to moderate benefits (15,19). One such study utilized resistance-trained individuals, assessing muscular endurance at 70% 1RM, after consuming either a placebo, MIPS, or a MIPS with the addition of p-synephrine (i.e., citrus aurantium) (15). P-synephrine, which acts as a stimulatory agent of the sympathetic nervous system, may increase energy expenditure, fat oxidation, and promote an increase in athletic performance (41). Findings revealed a greater mean lifting volume (i.e., repetitions x load lifted) for both the MIPS (bench: 5.8%; leg press: 7.9%) and MIPS (bench: 8.6%; leg press: 1.6%) with p-synephrine (15). However, the difference in overall volume represents an additional ~1 – 3 repetitions on the final set; thus, results should be interpreted with caution.

For muscular strength, four weeks of MIPS ingestion prior to an exercise session demonstrated an increase in bench press (6%), squat (12%), and deadlift (9%) as compared to a placebo group (bench: 5%, squat: 8%, deadlift: 7%) in resistance-trained males with over a year of training experience (19). In contrast, Martinez et al. (20) demonstrated no effect of a MIPS on 1RM bench press, vertical jump, or medicine ball put. These studies represent a small sample on MIPS and the research consensus indicates a trivial-to-small benefit for muscular endurance and strength after MIPS consumption.

While a small amount of evidence exists for potential benefits when consuming a pre-workout supplement, inconsistencies within the literature still remain when considering the specific dosages, populations, and types of activities performed. However, not all interactions with dietary supplements are positive. Thus, individuals should be aware of the drawbacks, side effects, and contraindications prior to ingesting a pre-workout.

THE "BAD"

As previously indicated, the evidence on the effectiveness of pre-workout supplementation is inconsistent with an abundance of literature reporting no overall effect, and even decreases in performance (2,31). For example, a pre-workout containing whey protein, creatine, caffeine, citrulline malate, ginseng, and other compounds demonstrated no differences, as compared to a control group, in maximal oxygen consumption (VO_{2max}), anaerobic or aerobic running capacity, or body composition after three weeks of high-intensity interval training in moderately trained males (31). While most individuals improved general fitness (e.g., critical velocity and VO_{2max}) and body composition (e.g., decreased fat mass), results could not be specifically attributed to the dietary supplement. Furthermore, Cameron et al. (2) examined recreationally-active females (aged 21.5 ± 1.7 years) to determine the effects of a MIPS on resting measures (i.e., blood pressure, energy expenditure, and heart rate), as well as muscular endurance, sprint performance, and dynamic power (i.e., countermovement jump). The MIPS included a proprietary blend of various compounds including (but not limited to) beta alanine, l-tyrosine, l-glycine, taurine, l-carnitine base, beet root extract, and caffeine anhydrous (100 mg). Results demonstrated trivial-to-no mean differences between the MIPS and placebo in energy expenditure (~81 kcal/day), systolic blood pressure, 25-s sprint performance (<1 m), muscular endurance, focus, or countermovement jump. While these findings demonstrate the large inter-individual responses to MIPS use, information more often overlooked when consuming dietary supplements are the side effects and underlying risks.

From digestive upsets to acute myocardial infarction and hemorrhagic stroke, pre-workout should not be casually added to an individuals' routine without further examination of the ingredients, possible side effects, and one's medical history. Dietary supplements, as a whole, are estimated to account for ~23,000 emergency department visits each year, with ~2,000 of those requiring hospitalization (8). From those hospital visits, weight loss, bodybuilding, and "energy" products (including pre-workout) accounted for ~72%, with the majority of adverse effects including chest pains, tachycardia, and heart palpitations (8). A small list of side effects for common pre-workout supplement ingredients have been provided in Table 1.

Like all dietary supplements, pre-workouts can be manufactured, labeled, and marked as a "proprietary blend" of ingredients without regulation by the Food and Drug Administration (FDA) prior to its release to the market. Thus, a large majority of products reach consumers without undergoing a proper laboratory analysis to establish the safety, efficacy, and proper dosage of each ingredient. While pre-workout supplements are designed to alter the rate at which physiological systems function, when combined with exercise, individuals are more likely to experience an increase in negative effects that could potentially inflict stress on the body as a whole (8). Individuals should consume no more than the recommended serving size of a pre-workout supplement, as overconsumption may lead to nausea, skin irritation, shortness of breath, irregular heartbeat, or heart attack (8,27). However, suggested serving size labels do not account for the consumers' age, physical activity level, underlying medical conditions, or psychological disorders. As such, individuals suffering from

a cardiovascular, metabolic, endocrine, neuromuscular, or psychological disorder are not advised to consume any form of pre-workout supplement as this could cause an individual's condition to worsen or interfere with treatment. While this list is not exhaustive, people should consult with a physician prior to consumption.

The inclusion of various ingredients within a "pre-workout" can potentially provoke an unwanted response; however, individuals should also be aware of the possible inclusion of a banned substance or compounds added to reduce the overall quality of a product (i.e., adulterated). Within a 10-year span (from 2007 to 2016), the FDA identified almost 800 supplements containing compounds that had either been banned for general sale (i.e., prescription only) or were illegal (34). One such compound, 1,3-dimethylamylamine (DMAA), is a potent vasoconstrictor with side effects such as shortness of breath, increased blood pressure, and arrhythmias, and has been shown to be a known cause of strokes and heart attacks (7). DMAA has been illegal as a dietary supplement since 2013; although, it is occasionally found in supplements sold to the general population (4,27). Furthermore, a large proportion (i.e., ~50%) of the altered products were targeted for weight loss or muscle building, with 20% containing two or more hidden ingredients. For instance, an International Olympic Committee examination of 634 dietary supplements indicated that ~15% of the sample tested positive for anabolic steroids (9).

Even if a supplement is cleared by a testing facility as not containing a banned or adulterated substance, it does not guarantee that the next batch will be cleared. A study examining the re-testing of dietary supplements, six months post-determination of a banned substance, found that 63% still contained the same marked ingredient (3). Furthermore, when supplements were re-tested, 22% contained a different banned compound not originally identified. Therefore, athletes should use a trusted verification and third-party testing source, as well as consult their respective sponsoring organization (e.g., NCAA, Olympic Federation) for a list of approved versus banned substances and ingredients prior to consumption. While proper safety precautions should be taken before consuming a pre-workout supplement, risks still remain for individuals, regardless of health status, with rare incidents ending in serious illness or death. Thus, let us examine three cases of such occurrences.

THE "UGLY"

The following information consists of a small sample of documented case reports involving the "ugly" (and unfortunate) cost of dietary supplementation consumption.

Case Report #1 (4): Two U.S. active-duty soldiers experienced severe adverse effects from the regular consumption of dietary supplements containing DMAA. Both individuals had an increased core body temperature (i.e., ~105°F) despite low environmental temperatures (i.e., ~73 – 75°F) as well as leg cramps and dyspnea prior to loss of consciousness and ultimately resulted in death for both. While one soldier died shortly after the initial syncope (~4 hr), the second individual developed multiple organ failure and rhabdomyolysis leading to death five weeks after the initial event.

Case Report #2 (27): A marathon runner completing the final portion of the 2012 London Marathon suddenly collapsed and died shortly after. It was reported that the runner was supplementing with one scoop of a pre-workout compound containing DMAA during the race. The increased exertion combined with the potent vasoconstrictor, caused acute cardiac failure.

Case Report #3 (12): An otherwise healthy 25-year-old active-duty airman with no past medical history or not currently taking any medications consumed two servings of a pre-workout supplement prior to a workout. The individual performed their typical moderate-intensity weightlifting routine; however, within an hour, the person developed a severe headache, double-vision, and loss of balance and motor control. An emergency care center determined that the person suffered a hemorrhagic stroke requiring surgical intervention. While the hemorrhagic stroke was directly attributed to the pre-workout, the specific supplement contained ingredients (e.g., caffeine and β-phenethylamine) previously associated with adverse effects, including strokes.

CONCLUSIONS

Based upon the current literature, pre-workout supplementation, whether single- or multi-ingredient, has demonstrated slight increases in perceived energy, focus, power, and time-to-exhaustion, as well as decreases in perceived effort and reaction time. While supplementation, particularly pre-workout, has risen dramatically from previous years, practitioners should be aware of the advantages and disadvantages for each ingredient. Due to variations in physiological response, addition of banned compounds, and underlying contraindications, individuals should consult a physician before consuming any dietary supplement.

TABLE 1. DESCRIPTIVE ANALYSIS OF THE BENEFITS, DOSAGES, AND SIDE-EFFECTS OF COMMON PRE-WORKOUT SUPPLEMENT INGREDIENTS

INGREDIENT	WHAT IT DOES IN THE BODY	POTENTIAL BENEFITS	OPTIMAL DOSAGE	SIDE EFFECTS	CONTRA-INDICATORS
Beta-alanine Non-essential amino acid	Improves muscle and blood pH buffering capacity.	**Increased:** • Time to exhaustion • Muscular endurance • Anaerobic capacity • Lean mass • Lactate threshold **Decreased:** • Fat mass • Fatigue (17)	4 – 6 g/day (33)	• Paresthesia (tingling) • Gastrointestinal distress (often with doses >20 g)	• Should not be taken when pregnant or breast-feeding • May cause taurine deficiency in high doses (>20 g)
Caffeine Central nervous system stimulant	Inhibits adenosine receptors.	**Increased:** • Time to exhaustion • Muscular endurance • Calcium release • Blood glucose levels • Fat utilization **Decreased:** • Fatigue (10)	3 – 6 mg/kg bodyweight 60 min prior to exercise (10)	• Tremors • Insomnia • Tachycardia • Headache • Gastrointestinal distress	Should not be taken with: • Stimulant medications • Anticoagulants • Monoamine oxidase inhibitors • Quinolone antibiotics
Citrulline Malate Non-essential amino acid	Increases plasma levels of arginine, ammonia recycling, and nitric oxide metabolism.	**Increased:** • Oxidative energy turnover • Nitric oxide synthesis • Rate of phosphocreatine recovery • Repetitions to fatigue **Decreased:** • Muscle fatigue • Muscle soreness • Blood pressure (26)	4 – 10 g 60 min prior to exercise (26)	• Gastrointestinal distress • Diarrhea	Should not be taken with: • Nitrates • Antihypertensive medications • Erectile dysfunction medications This combination may cause a dangerous drop in blood pressure. • Should not be taken when pregnant or breast-feeding

TABLE 1. DESCRIPTIVE ANALYSIS OF THE BENEFITS, DOSAGES, AND SIDE-EFFECTS OF COMMON PRE-WORKOUT SUPPLEMENT INGREDIENTS (CONTINUED)

INGREDIENT	WHAT IT DOES IN THE BODY	POTENTIAL BENEFITS	OPTIMAL DOSAGE	SIDE EFFECTS	CONTRA-INDICATORS
Cobalamin Vitamin B-12	Essential for red blood cell production, cell metabolism, nerve function, and the production of DNA.	**Decreased:** • Plasma homocysteine levels • Fatigue (6)	0.5 – 1 mg/day (6) *Vitamin B12 has a low absorption rate	• Acne High doses (>1 mg) can cause: • Dizziness • Headache • Anxiety • Nausea • Vomiting	Should not be taken with: • Anticonvulsants • Chemotherapy medications • Proton pump inhibitors • H2 blockers • Colchicine • Metformin • Tetracycline This combination may interfere with B-12 absorption. • Do not take if allergic or sensitive to cobalt
Creatine Nitrogen-containing compound synthesized from amino acids	Aids in replenishing energy stores through the rapid rephosphorylation of ADP to ATP.	**Increased:** • Creatine content in muscles • Power output • Strength • Anaerobic running capacity • Total body water • Glycogen resynthesis **Decreased:** • Symptoms of depression • Fatigue (1,18)	3 – 5 g/day (1)	• Gastrointestinal distress (often with doses >10 g) • Nausea • Diarrhea • Water retention	• Should not be taken when pregnant or breast-feeding • Caffeine may decrease the efficacy of creatine

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INGREDIENT	WHAT IT DOES IN THE BODY	POTENTIAL BENEFITS	OPTIMAL DOSAGE	SIDE EFFECTS	CONTRA-INDICATORS
L-Arginine Conditionally essential amino acid	Increases nitric oxide activity (vasodilation), in turn increasing blood flow.	**Increased:** • Anaerobic capacity **Decreased:** • Blood pressure • O^2 cost to working skeletal muscle tissue during low- to moderate-intensity exercise (5) *Benefits based on L-arginine synthesized within the body, not supplementation*	3 – 7 g per serving (5)	• Worsening of asthma symptoms • Nausea • Abdominal pain • Diarrhea (often with doses >10 g) • Bloating • Gout • Increases in allergic reactions	Should not be taken with: • Anticoagulants • Antihypertensive medications • Beta adrenergic agonists • Nitrates • These combinations may increase the risk of bleeding, reductions in blood clotting, and decrease in blood pressure. Should be avoided for those with liver cirrhosis and kidney disorders.
Niacin Vitamin B-3	Aids enzymes to convert food into energy. Effective at normalizing blood lipid levels.	**Increased:** • High-density lipoprotein (HDL) level • Fasting glucose concentrations **Decreased:** • Low-density lipoprotein (LDL) level • Triglyceride • Insulin sensitivity (16)	500 – 1,000 mg/day (16)	• Itching • Skin flushing • Headache • Dizziness High doses (>1,500 mg) can cause: • Fatigue • Impaired vision • Nausea • Vomiting • Abdominal pain • Liver damage • Tachycardia	Should not be taken with: • Alcohol • Anticoagulants • Antihypertensive medications • Tuberculosis medications • Diabetes medications These combinations may increase the risk of liver damage, bleeding, and may decrease blood pressure.
Pyridoxine Vitamin B-6	Assists in the growth and development of red blood cells and motor neurons, as well as regulates water excretion. Works as a coenzyme in glycogen and amino acid metabolism.	**Increased:** • Vascular functioning • Oxidation of carbohydrates and fats **Decreased:** • Plasma homocysteine levels (6,24)	100 mg/day (6,24)	• Headache • Nausea • Drowsiness High doses (>1,000 mg) can cause: • Ataxia • Sensory neuropathy • Numbness • Painful skin lesions • Heartburn • Photosensitivity	Should not be taken with: • Altretamine • Barbiturates • Levodopa This combination may increase rate of drug breakdown; thus, decreasing efficacy.

TABLE 1. DESCRIPTIVE ANALYSIS OF THE BENEFITS, DOSAGES, AND SIDE-EFFECTS OF COMMON PRE-WORKOUT SUPPLEMENT INGREDIENTS (CONTINUED)

INGREDIENT	WHAT IT DOES IN THE BODY	POTENTIAL BENEFITS	OPTIMAL DOSAGE	SIDE EFFECTS	CONTRA-INDICATORS
Sodium Bicarbonate Salt compound	Promotes acid-base regulation	**Increased:** • Anaerobic capacity **Decreased:** • Blood pH (13)	300 mg/kg bodyweight 60 min prior to exercise (13)	High doses (>500 mg/kg) can cause: • Gastrointestinal distress • Headache • Restlessness • Increased edema	Should not be taken when pregnant or breast-feeding Should not be taken with: • NSAIDs • Antibiotics • Mesalamines Should be avoided for individuals with impaired renal function
Taurine Amino sulfonic acid	Aids in the development of the central nervous system, synthesis of bile salts, and regulates electrolytes osmolality.	Increased: • Blood flow • ATP synthesis Decreased: • Arterial stiffness • Oxidative stress (22)	500 – 3,000 mg/day (29)	• Itching • Nausea • Dizziness	• Should not be taken when pregnant or breast-feeding • Avoid taking with large quantities of caffeine (>6 mg/kg of bodyweight)
Tyrosine Non-essential amino acid	Precursor to catecholamines and increases synthesis of dopamine, epinephrine, and norepinephrine.	**Increased:** • Memory (under cold- or noise-induced stress) • Cognitive functioning (under cold- or noise-induced stress) **Decreased:** • Fatigue (under cold-induced stress) (25)	500 – 2,000 mg 60 min prior to exercise (25)	• Nausea • Headache • Heartburn	Should not be taken with: • Levodopa • Monoamine oxidase inhibitors (These combinations may decrease drug absorption and efficacy) Do not consume if: • Pregnant or breast-feeding • Individuals have hyperthyroidism or Graves' disease (may increase thyroxine levels)

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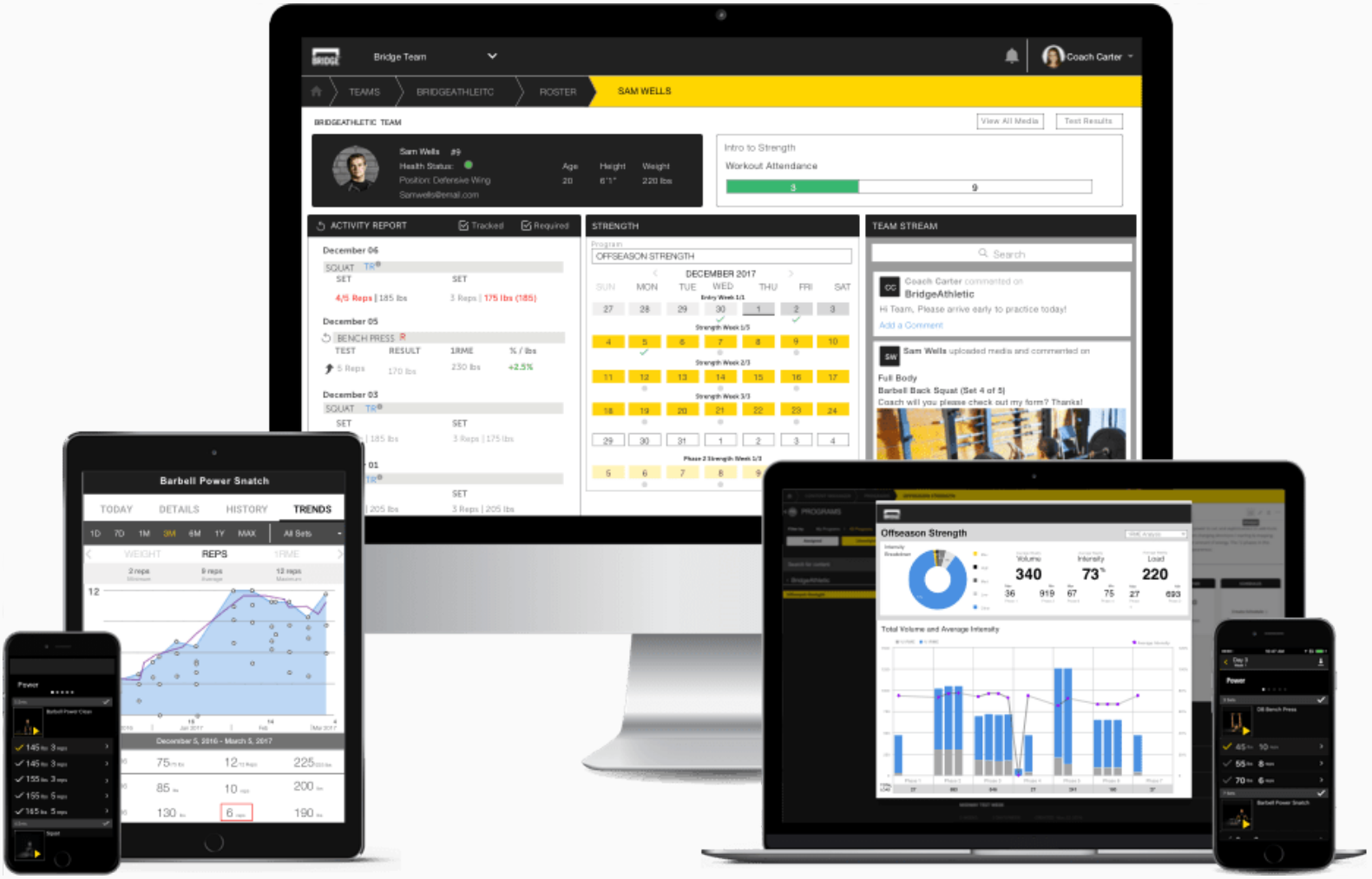

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