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Tomato genotype but not crop water deficit matters for tomato health benefits in diet-induced obesity of C57BL/6JRj male mice

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ABSTRACT

Several studies have linked the intake of lycopene and/or tomato products with improved metabolic health under obesogenic regime. The aim was to evaluate the differential impact of supplementations with several tomato genotypes differing in carotenoid content and subjected to different irrigation levels on obesity-associated disorders in mice. In this study, 80 male C57BL/6JRj mice were assigned into 8 groups to receive: control diet, high fat diet, high fat diet supplemented at 5 % w/w with 4 tomato powders originating from different tomato genotypes cultivated under control irrigation: H1311, M82, IL6-2, IL12-4. Among the 4 genotypes, 2 were also cultivated under deficit irrigation, reducing the irrigation water supply by 50 % from anthesis to fruit harvest. In controlled irrigation treatment, all genotypes significantly improved fasting glycemia and three of them significantly lowered liver lipids content after 12 weeks of supplementation. In addition, IL6-2 genotype, rich in β-carotene, significantly limited animal adiposity, body weight gain and improved glucose homeostasis as highlighted in glucose and insulin tolerance tests. No consistent beneficial or detrimental impact of deficit irrigation to tomato promoting health benefits was found. These findings imply that the choice of tomato genotype can significantly alter the composition of fruit carotenoids and phytochemicals, thereby influencing the anti-obesogenic effects of the fruit. In contrast, deficit irrigation appears to have an overall insignificant impact on enhancing the health benefits of tomato powder in this context, particularly when compared to the genotype-related variations in carotenoid content.

1. Introduction

Obesity is a growing health concern and is associated with an increased risk of chronic diseases such as insulin resistance, type 2 diabetes, non-alcoholic fatty liver disease, cardiovascular disease, and certain types of cancer (Lobstein, Brinsden, & Neveux, 2022; Piché, Tchernof, & Després, 2020; Polyzos, Kechagias, & Tsochatzis, 2021). In this context, diet plays a crucial role in developing and preventing obesity and related health conditions (Veit, van Asten, Olie, & Prinz, 2022). Several studies point out that a diet overall rich in fruits and vegetables improve health status and reduce the risk of obesity or metabolic syndrome (K. He et al., 2004; M. Lee, Lim, & Kim, 2019; Nguyen, Oh, & Kim, 2022). Tomatoes (*Solanum lycopersicum*) are important contributors of fruits and vegetables consumption with a wide diversity of fresh and derived products (juice, concentrate…). Tomatoes have been shown to possess several health benefits, including anti-inflammatory and antioxidant properties (Canene-Adams, Campbell, Zaripheh, Jeffery, & Erdman, 2005; Landrier et al., 2023; Li et al., 2018). In this context, carotenoids have been targeted as important candidates to provide anti-obesity effects implying adipose tissue (Mounien, Tourniaire, & Landrier, 2019). Tomatoes can be remarkable source of lycopene, which has been suggested to participate in the fruit health benefits in a context of obesity-related metabolic diseases (Bohn et al., 2021; Senkus, Tan, & Crowe-White, 2019; Zhu et al., 2020). Additionally,

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tomatoes are a rich source of other carotenoids including β-carotene and colorless carotenoids phytoene and phytofluene (Mapelli-Brahm & Meléndez-Martínez, 2021). Depending on the genotype, lycopene is not necessarily the main carotenoid accumulated in the fruit (Flores, Sánchez, Fenoll, & Hellín, 2017). Tomatoes are also an interesting source of other beneficial compounds such as ascorbic acid, phenolic compounds, minerals and alcohol insoluble matter (AIM) also known as insoluble dietary fibers. It is important to acknowledge that the combined activity of various phytochemicals cited above may enhance the health benefits of tomatoes through additive or synergistic effects (Basu & Imrhan, 2007; Fenni et al., 2017). Very little attention is usually given on genotype and/or growth conditions of tomato and tomato derived materials in animal supplementation studies (Fenni et al., 2017; Lee et al., 2015; Li et al., 2018; Tan et al., 2014). It is however known that genotype and environment can significantly change fruit nutrient content (Flores et al., 2017; Kavitha et al., 2014). Several agronomic factors such as crop genotype, daily temperature, drought, light spectrum or fertilization have been described to have a significant impact of fruit carotenoids and phenolics (total or specific compounds) (Poiroux-Gonord et al., 2010). For example, it is possible to obtain up to 25 times the concentration in β-carotene of conventional tomato varieties with breeding. Similarly, high solar light exposure for 5 h can increase more than 2 times tomato total phenolic compounds (Poiroux-Gonord et al., 2010). Among agronomic factors, drought or deficit irrigation (DI) have been identified as a possible lever to enhance sustainability of food production by reducing water inputs, and possibly improve fruit health benefits (Lu et al., 2021; Ripoll et al., 2014). DI triggers a physiological stress response from the plant that has been described to have a positive effect on fruit quality with increased secondary metabolites content (Hou, Zhang, Du, Kang, & Davies, 2020; Ripoll et al., 2014). In a water deficit context, it is expected that the nutrient concentration in fresh fruit increases compared with the control (non-limiting) irrigation (CI) treatment (Petrović et al., 2019; Ripoll, Urban, Brunel, & Bertin, 2016). This mostly results from a concentration effect due to the decrease of water accumulation under DI, while it is unclear whether nutrient increase is also observed on a dry weight basis (Ripoll et al., 2016). To our knowledge, clinical or preclinical supplementation studies have not examined the impact of possible changes on fruit health benefits of various tomato genotypes and/or water deficit. This is particularly striking since many agronomic research report the impact of genotype and environment or processing interactions on fruit quality, but this rarely translates into health benefits evaluation (Tilesi, Lombardi, & Mazzucato, 2021).

In this study, we investigated the metabolic health outcomes observed in a cohort of C57BL/6JRj male mice subjected to an obesogenic regime supplemented with several tomato powders differing in genotype and/or irrigation regime. In the scope of our research was targeted metabolic health, with a focus on body weight gain, adiposity, liver lipids and glucose homeostasis through glucose and insulin tolerance tests. The originality of our work lies in the fact that tomato fruits were produced in similar controlled conditions before incorporation in the animal diet and displayed contrasted carotenoid content. We hypothesized that the animal metabolic health status may be dependent on the tomato genotype and that stronger positive health benefits may emerge from high lycopene/high total carotenoids tomatoes. In addition, we selected 2 tomato genotypes also produced under DI, tested to determine whether DI could modulate and possibly improve health benefits.

2. Experimental section

2.1. Tomato source and incorporation in food pellets

Two processing tomato genotypes (H1311, M82) and two introgression lines originating from a cross between M82 and the wild green fruited *S. pennellii* were chosen (IL6-2, IL12-4) (Eshed & Zamir, 1995), based on their contrasted carotenoid content. Plants were grown in a greenhouse (Avignon, France) with a dripping system providing water and nutrients. All plants were sown under control irrigation (CI), where root humidity was maintained at soil capacity. Prior to the occurrence of the first anthesis, plants homogeneous in size and leaf number were randomly distributed into two irrigation treatments. The first group stayed under CI during the whole fruiting period. The second group was exposed to deficit irrigation (DI) resulting in a 50 % reduction of water supply volume compared to the control treatment. Fruits that displayed blossom end rot were discarded, and healthy fruits were harvested when maturity was reached. At harvest, fruits were cut into ~1 cm^3 pieces, cryogrinded, and stored in sealed bags at −80 °C. At the end of harvest period, all tomato samples were freeze-dried and stored at 4 °C safe from light. Soluble sugars, starch, organic acids, ascorbic acid, carotenoids and polyphenols (Supplemental Table 1) were characterized as previously described (Ruiz-Nieves, Ayala-Garay, Serra, Dumont, Vercambre, Génard, & Gautier, 2021). AIMs were quantified as previously described (Musse et al., 2021). Carotenoids were assessed on the freeze-dried tomato powders before incorporation into the pellets. The powder is extracted with a hexane-dichloromethane-ethyl acetate mixture (1:4:50 v:v:v) and then assayed by HPLC as described elsewhere (Sérino, Gomez, Costagliola, & Gautier, 2009). Briefly, the assay was performed using with a DAD UV–visible detector (surveyor PDA plus detector, Thermo Electron 355 river Oaks Parkway San Jose, CA USA) under the following conditions: coupling of two columns, Chromolith Performance RP-18e column (100 × 4.6 mm, Merck, VWR International, Fontenay-sous-Bois, France); guard cartridge, Chromolith RP-18e (10 * 4.6 mm Merck, VWR International); column oven temperature, 28 °C; mobile phase, Acetonitrile/Ultra Pure water/ethyl acetate (53:7:40, v/v/v); flow rate of mobile phase, 1 mL/min; injection volume, 5 μL; five working wavelengths, 474 nm for lycopene, 454 nm for β-carotene, 286 nm for phytoene, 350 nm for phytofluene, and 448 nm for lutein. The tomato powders were homogeneously incorporated in high fat diet (HFD) food pellets with a mixing screw (251HF, 45.9 % energy from lipids, 21 % sucrose, U8954 Version 204, from SAFE Custom Diets®) (Supplementary Table 2). The regimes were constituted as follows: HFD-supplemented 5 % weight with tomato powder, namely HFD + 5 % H1311 tomato grown under CI (H1311-CI) or DI (H1311-DI), HFD + 5 % M82 tomato grown under CI (M82-CI) or DI (M82-DI), HFD + 5 % IL6-2 tomato grown under CI (IL6-2-CI) and HFD + 5 % IL12-4 tomato grown under CI (IL12-4-CI).

2.2. Animal experiments

All procedures were performed in accordance with the local Ethics committee and the cell in charge of animals used for scientific experiments by the French ministry of Higher Education, Research and Innovation (APAFIS #34349–2021121310395407). Eighty C57BL/6JRj seven-week-old male mice (Roger Janvier Labs, Le Genest Saint Isle, France) were fed with control purified diet (CD) food (AIN93-G, 17.4 % energy from lipids, 12 % sucrose, U8978 Version 22, from SAFE Custom Diets®, France) (Supplementary Table 1) and for a 1-week acclimatization period. Before diet change and after the 1-week acclimatization period, all the animals were weighted (22.2 ± 1.3 g) and cage repartition between groups (N = 10 per group) was organized to maximize the homogeneity of mean and standard deviation of mouse weight between groups (Bartlett's test p-value for diet effect = 0.92, ANOVA p-value for diet effect = 0.99). The mice were assigned into one of the eight experimental groups depending on their diet: CD, HFD, or HFD + 5 % weight freeze-dried tomato powder. Mice were maintained at 22 °C in a 12:12 h light/dark cycle with *ad libitum* access to food and water during the whole experiment. Food pellets were stored in a fridge (+4 °C) in an airtight container before feeding and pellets were replaced in each cage every 3–4 days to maximize freshness. Each mouse was weighted once a week and dietary intake was recorded on a 24 h time period by food weight difference, two times for each cage during the whole experiment.

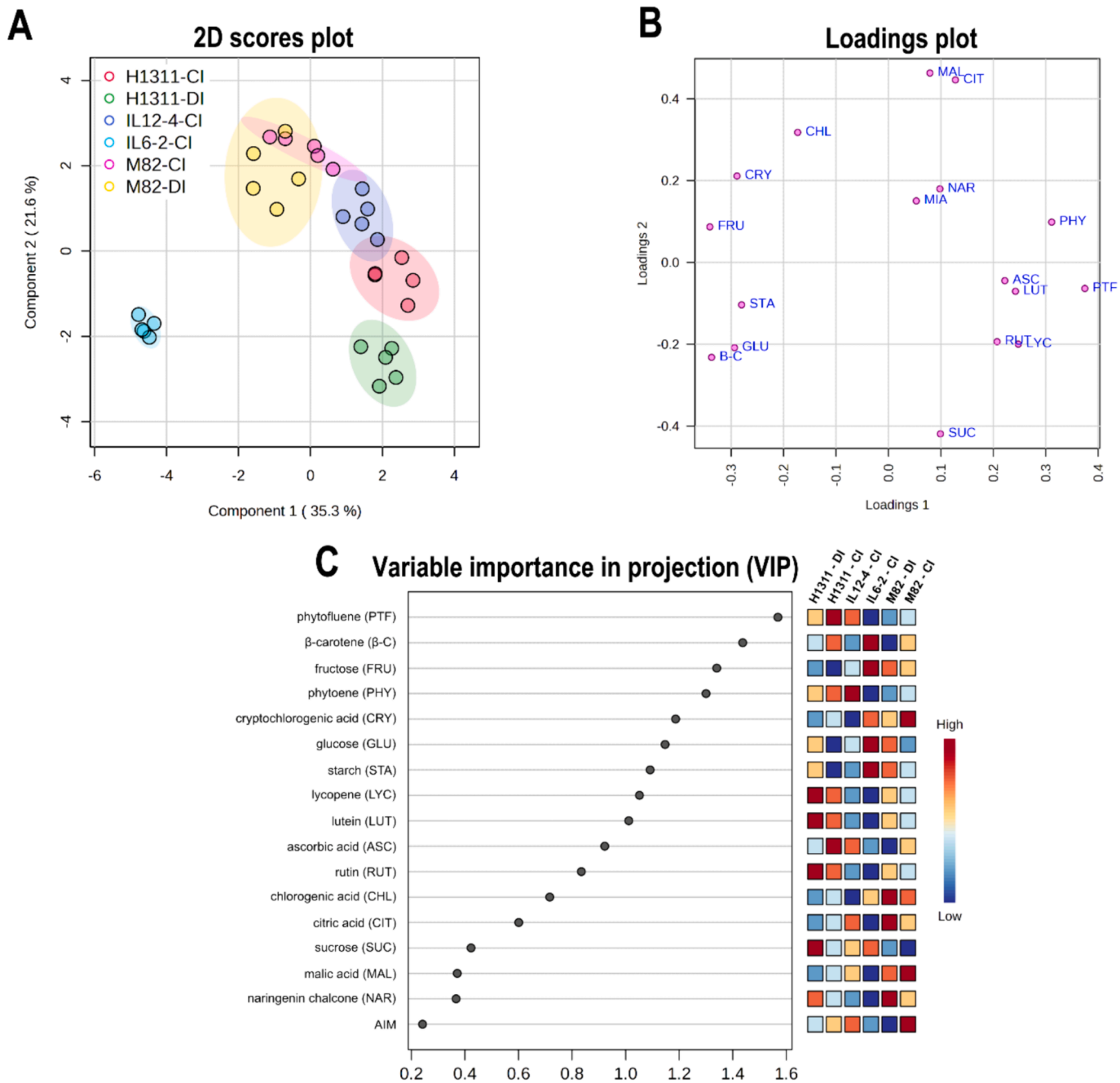

Fig. 1. Partial least squares discriminant analysis (PLS-DA), with 2D scores plot (A), loadings (B) and variable importance in projection (VIP) scores with ranking of the tomato powder in terms of mean compound concentration (color scale) (C), for the four tomato genotypes tested under Control Irrigation (CI) (H1311-CI, M82-CI, IL6-2 CI and IL12-4 CI) and the two tomato genotypes tested under Deficit Irrigation (DI) (H1311-DI and M82-DI). Loadings plot variable names are indicated in brackets after compound name in the VIP plot. AIM = alcohol insoluble matter.

After 12 weeks, the mice were fasted overnight and organs and blood were collected by cardiac puncture in heparinized tubes using a general anesthetic (Sevoflurane, Baxter, France). Animals were euthanized by cervical dislocation under anesthesia. The plasma was isolated by centrifugation at 2000 g for 15 min at 4 °C and was stored at −80 °C until analysis. Mouse liver, retroperitoneal, epididymal, and subcutaneous adipose tissue (AT) deposits were collected, weighed, snap-frozen and stored at −80 °C until analysis.

2.2.1. *Oral glucose and insulin tolerance tests*

Insulin and glucose tolerance tests were performed respectively 9 and 10 weeks after diet differentiation. For the insulin tolerance test, all mice were fasted for 6 h and injected *i.p.* with 0.5 IU/kg fast-acting insulin (NovoRapid, novo nordisk). For the glucose tolerance test, all mice were fasted for 12 h and gavaged with 2 g/kg D-(+)-glucose (Millipore Sigma). For both tests, blood samples were taken from the tail tips at specific time intervals (T_0 (fasting), $T_0 + 15$ min, $T_0 + 30$ min, $T_0 + 60$ min, $T_0 + 90$ min, $T_0 + 120$ min) to measure glucose levels (Accu-Check glucometer, Roche). Glucose and insulin tolerance levels were assessed by computing the trapezoidal area under the response curve (Cardinault et al., 2020).

2.2.2. *Biochemical analyses*

The plasma glucose was evaluated using glucose RTU (bioMerieux,

France). Triglycerides and free fatty acids (FFA) were measured using a colorimetric test (RANDOX, Crumlin, Co. Antrim, UK). Insulinemia was measured using an enzyme-linked immunosorbent assay ELISA (ALPCO Diagnostics, New Hampshire, USA). The HOMA-IR index was calculated according to the following formula: fasting insulin (mIU/L) × fasting glucose (mmol/L)/22.5.

2.2.3. Liver lipid quantification

Total liver lipids were determined gravimetrically with ~0.20 g of liver sample. Samples were weighted and grinded in bead tubes for two 30-second cycles at 30 Hz in a Retch grinder (Brinkman Instruments Inc.) with a mixture of 1 mL methyl-*tert*-butyl ether (MTBE) and methanol (10:3; v/v) in a 1.5 mL tube. Phosphate Buffer Saline (PBS 1X) was added to induce phase separation (final MTBE/methanol/PBS ratio of 10:3:2.5, [v/v/v]) (Matyash, Liebisch, Kurzchalia, Shevchenko, & Schwudke, 2008). The solution was centrifugated at 3000 g for 10 min at 4 °C. The upper phase (MTBE) containing lipids was evaporated in a pre-tared tube under nitrogen flow gas and the extraction procedure was repeated twice. After complete drying, the total lipid content of the liver was obtained by calculating the ratio between the weight of the film stuck to the walls of the tube and the liver sample weight. Validation was carried out with lipids quantification of a commercial food sample (AIN93-G, U8978 Version 22, from SAFE Custom Diets®, France) with known total lipid content.

2.2.4. Adipose tissue gene expression

Total RNA was extracted from epididymal AT using TRIzol reagent (Thermo Fischer Scientific) according to the manufacturer protocol. The cDNA was synthesized from 1 μg of total RNA using random primers and Moloney murine leukemia virus reverse transcriptase (Landrier, Reboul, Amiot, & Borel, 2008). Real-time quantitative PCR analyses were performed using the Roche LightCycler® 480 PCR System (Derghal et al., 2018). For each condition, expression was quantified in duplicate, and 18S mRNA was used as the endogenous control in the comparative cycle threshold method (C_T) and data was expressed as relative expression ratio.

2.2.5. Statistical analysis

Unless specified, all data are expressed as mean ± SEM. Significant differences between the control and other groups were determined using one-way ANOVA to test diet effect. Significant diet effect ($p < 0.05$) was followed by Fisher-exact test with Benjamini-Hochberg multiple-testing correction. The Benjamini-Hochberg procedure help control the false discovery rate (FDR) in a context where multiple hypothesis tests are performed simultaneously to compare the outcomes between mice groups. Controlled p values < 0.05 were considered as significant outcomes between groups. Plots and statistics were performed using GraphPad (GraphPad Prism version 9.0.0, GraphPad Software) or R software (R Core Team 2022). PLS-DA analysis on tomato powder composition was performed online with one factor statistical analysis on auto centered data using MetaboAnalyst (Pang et al., 2022).

3. Results

3.1. Tomato composition is highly discriminated by phytochemicals

Beyond carotenoids, sugars, acids, phenolics and AIM were also quantified in freeze-dried tomato powders. Based on the 2D scores plot (Fig. 1, A), the partial least square discriminant analysis (PLS-DA) of compounds between groups revealed a stronger discrimination of tomato samples based on genotype rather than water deficit treatment for the two genotypes tested under DI (H1311, M82). The most discriminated compounds between all groups were phytofluene, β-carotene and fructose. AIM, naringenin chalcone and malic acid remained mostly stable between powders. A relative ranking based on compound concentration on a dry mass basis was established between tomatoes (Fig. 1, B and C). Compared to the other genotypes, IL6-2 tomato was particularly rich in β-carotene, with an average 9.2-fold increase content compared with other CI tomatoes (Fig. 1, Table 1). IL6-2 also distributed the highest content of sugars compared to other genotypes, with an average 1.2-fold increase compared to other CI tomatoes. Total sugar fruit composition can be approximated to 49.2 % glucose, 46.7 % fructose and 1.5 % sucrose on average for all CI tomatoes, all sugars constituting on average 35.3 % of CI fruit dry weight (data not shown). Considering mice food intake and the carotenoid content of freeze-dried tomato powders, we estimated the dietary carotenoid intake of mice supplemented at 5 % of tomato powder in their food diet (Table 1). Overall, H1311 regimes (CI and DI) could be considered as high total carotenoid regimes, driven by a high lycopene content, which was expected for this high lycopene cultivar (Ozminkowski, 2015). IL12-4 stands out as a high phytoene and phytofluene source and IL6-2 stands out as a high β-carotene source (Table 1). DI resulted in a marked lycopene increase and total carotenoid intake for H1311 but not statistically significant for the M82 genotype. DI did not lead to a significant increase of lutein intake for both genotypes. Phytoene, phytofluene and β-carotene intakes displayed a low insignificant decrease under DI for both genotypes.

Table 1
Carotenoid intake estimation (μg/mouse/day ± SD (σ)). Mean intake was calculated from the mean carotenoid content of freeze-dried tomato powder incorporated in the food pellets * mean food intake consumption per mouse per day (Fig. 2D) * 5 % tomato inclusion in food pellets. Letters indicate significant differences ($p < 0.05$) between groups, adjusted for multiple comparison with Benjamini Hochberg false discovery rate procedure.

	HFD + H1311-CI	HFD + H1311-DI	HFD + M82-CI	HFD + M82-DI	HFD + IL6-2 CI	HFD + IL12-4 CI
Lycopene	223.0 ± 39.0b	327.6 ± 75.1 a	165.5 ± 29.7c	173.7 ± 43.0c	93.2 ± 17.7 d	104.7 ± 17.3 d
Phytoene	92.3 ± 17.7b	78.2 ± 15.9 bc	66.5 ± 12.2 cd	54.6 ± 12.4 d	18.5 ± 2.9 e	150.7 ± 23.8 a
Phytofluene	16.9 ± 3.0 a	15.1 ± 3.1 a	8.1 ± 1.5 ab	6.7 ± 1.5 ab	2.5 ± 0.5b	17.7 ± 3.1 a
β-carotene	7.6 ± 1.3b	6.0 ± 1.2b	5.8 ± 1.32b	4.5 ± 1.0b	52.0 ± 9.2 a	4.9 ± 0.8b
Lutein	2.1 ± 0.4 a	2.3 ± 0.6 a	1.7 ± 0.3 a	1.8 ± 0.4 a	1.0 ± 0.2 a	1.1 ± 0.2 a
Total (sum)	341.9 ± 43.0b	429.3 ± 76.9 a	247.5 ± 32.1c	241.4 ± 44.7c	167.1 ± 20.2 d	279.1 ± 29.6c

3.2. Tomato genotypes differentially impact morphometry and mRNA levels

At the end of the 12 weeks supplementation period, mice body weight differed significantly between diets, with a significant average increase of body weight of +33.8 % between CD and all HFD diets including or not tomato powder (Fig. 2A, 2B). However significant lower body weight gain was observed for IL6-2 supplemented group only (−30.7 %, $p < 0.05$) (Fig. 2C), while other supplemented groups did not significantly differ from the HFD group. Food intake quantity was similar within the groups ($p = 0.94$) with an average food consumption of 2.7 g/mouse/day (Fig. 2D). Due to difference in diet energy load between control and HFD, average energy intake of HFD group significantly ($p < 0.05$) increased compared with energy intake of the CD group, whereas tomato supplemented groups energy intake did not significantly differ compared with energy intake of the HFD or CD group (Fig. 2E).

The decrease of body weight gain for IL6-2 group may be explained by a decrease of fat mass, as this group displayed lower amount of subcutaneous (−44.3 %, $p < 0.001$) and retroperitoneal (-38.6 %, p <

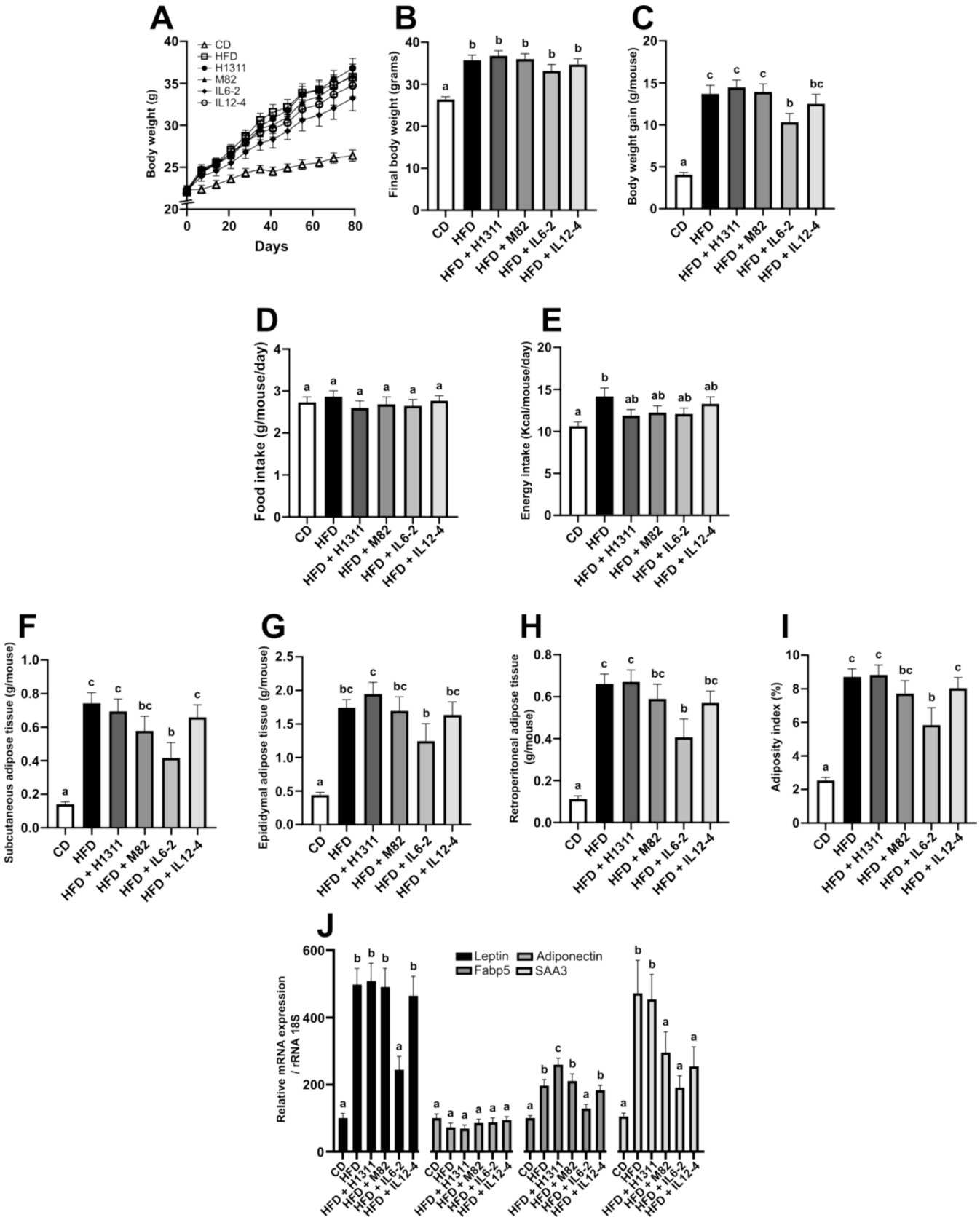

Fig. 2. Effect of tomato powder supplementation on mouse morphological parameters. Evolution of animal body weight during 12 weeks tomato supplementation (A) with description of final body weight (B) and body weight gain (C) before animal sacrifice. Food intake as quantity (D) and energy (E). After sacrifice, the subcutaneous (F), epididymal (G), retroperitoneal (H) adipose tissues were weighted to characterize the adiposity index (I). Values are means ± SEM (n = 10/group, except for D and E where n = 6/group). CD = Control diet; HFD = High-fat diet. Letters indicate significant differences ($p < 0.05$) between groups, adjusted for multiple comparison with Benjamini Hochberg false discovery rate procedure.

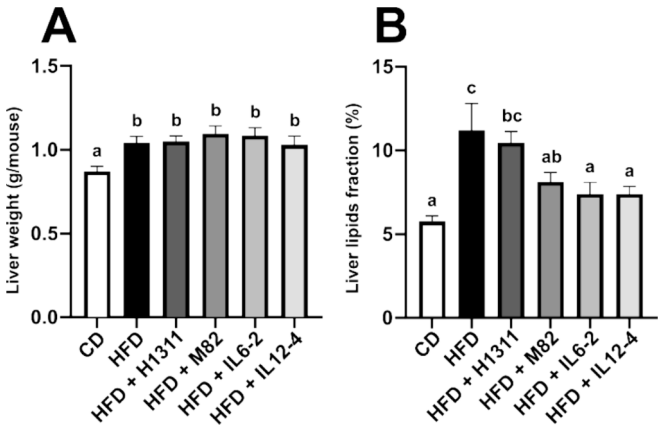

Fig. 3. Impact of tomato supplementation on mice liver weight (A) and liver lipids (B) after 12 weeks supplementation. Values are means ± SEM (n = 10/group). CD = Control diet; HFD = High fat Diet. Letters indicate significant differences ($p < 0.05$) between groups, adjusted for multiple comparison with Benjamini Hochberg false discovery rate procedure.

0.01) AT deposits compared with the HFD group (Fig. 2F, 2H). The decrease of AT deposit in the epididymal fat pad for IL6-2 supplemented group did not reach significance (−28.7 %, $p = 0.12$) compared with the HFD group. However, this decrease of AT deposits resulted into a significantly reduced adiposity index for IL6-2 group (−33.0 %, $p < 0.01$) compared with the HFD group (Fig. 2I). As expected, the HFD induced a strong increase of *Leptin*, *SAA3* (Serum Amyloid A3), acute-phase proteins related to metabolic inflammation (Maffei, Barone, Scabia, & Santini, 2016), and *FABP5* (Fatty Acid Binding Protein 5) mRNA compared to the CD (Fig. J). Among the tested powders, M82 and IL12-4 induced a significant decrease of *SAA3* mRNA compared to the HFD. IL6-2 induced a significant decrease of *Leptin*, *FABP5* and *SAA3* mRNA compared to the HFD (Fig. 2J). H1311 induced a significant increase of *FABP5* mRNA compared to the HFD. *Adiponectin* expression levels did not differ significantly between groups.

HFD and HFD+ tomato supplemented groups displayed significantly higher liver weight compared with the CD group (Fig. 3A). HFD increased liver lipids (+94.6 %, $p = 0.0001$) compared to the CD group (Fig. 3B), but tomato lowered liver lipid content significantly for M82 (−27.6 %, $p < 0.05$), IL6-2 and IL12-4 (−34.0 %, $p < 0.01$ respectively) compared with HFD. For these groups, mice liver lipid levels did not significantly differ from those of CD mice (Fig. 3B).

3.3. Tomato genotypes differentially improve glucose homeostasis and blood parameters

The HFD resulted in a significant increase in fasting glycemia compared with the CD group at 9 and 10 weeks after the diet start (Fig. 4A, D). The magnitude of this increase varied depending on the duration of fasting. Specifically, for a 6-hour fast, fasting blood glucose levels increased by +25.1 % ($p < 0.01$) (Fig. 4D), while for overnight fasting, the increase was much higher at +124.8 % ($p < 0.0001$) (Fig. 4A). Regardless of the genotype, tomato supplementation significantly reduced overnight fasting glycemia compared with the HFD group. The decrease in fasting glycemia ranged from −14.7 % ($p < 0.05$) for H1311 to −30.5 % ($p < 0.0001$) for M82 (Fig. 4A). However, for a shorter fasting period of 6 h, there was no statistically significant difference in fasting glycemia between the HFD and HFD + tomato supplemented groups (Fig. 4D).

The effect of tomato supplementation on glucose homeostasis was evaluated using OGTT and ITT tests. M82 and IL6-2 tomato genotypes supplementation improved ($p < 0.05$) glucose tolerance in OGTT as highlighted by the area under the curve (AUC) of the glycemic response (Fig. 4, B.2, B.3 and C) which was reduced compared with the AUC observed in the HFD animals. After 12 weeks, HFD diet induced an increase in fasting glycemia, insulinemia and HOMA-IR, and a decrease of all these parameters was observed only for IL6-2 supplemented group ($p < 0.05$) with no particular difference of blood triglycerides or non-esterified fatty acids concentrations observed between groups (Table 2). HFD significantly increased insulin resistance compared with the CD ($p < 0.0001$), evaluated using the AUC of the ITT blood glucose response curve, but no significant improvement was observed for tomato supplemented groups (Fig. 3, E.1 to E.4 and F) compared with the HFD group.

3.4. Tomato irrigation strategy does not improve tomato health effects

The effect of tomato supplementation on mice with M82 and H1311 tomato genotypes grown under CI was compared with the same genotypes grown under DI. Overall, no significant difference in health outcomes after the 12-week supplementation was observed on the measured parameters of the animals between the CI and the DI supplemented fruits (Figs. 5, 6, 7, Table 2), except for liver weight, with a significant increase was observed between H1311 CI and DI supplemented animals (+17.7 %, $p < 0.05$, Fig. 6A), but significant decrease of mice liver lipids (−28.1 %, $p < 0.01$, Fig. 6B). The increase of liver weight (+6.6 %, $p = 0.2$) and decrease of liver lipids (−12.1 %, $p = 0.4$) pattern under DI was observed for M82 genotype but the differences were not significant.

4. Discussion

The scope of this work was to evaluate the metabolic health benefits of tomato supplementation in a diet induced obesity mice model. In this first exploration of differential metabolic health driven by different tomatoes, it was chosen to conduct a wild phenotyping of mice, through several well-established parameters of metabolic health. Thus, the overall objective of this experimentation was to shed light on potential differences in terms of metabolic health at a macroscopic level. Six different tomatoes were selected to offer a contrast in carotenoid content, among which two powders were produced from fruits growing under a deficit irrigation treatment. The work was focused on key obesity markers such as body weight gain after 12 weeks supplementation, adiposity index, liver lipids, glucose homeostasis and blood parameters after sacrifice. Therefore, it was shown that tomato supplementation had beneficial or neutral effects on the parameters evaluated and that the number and amplitude of improvement highly depended on the tomato genotype.

In both CI and DI treatments, H1311 tomato powder provided important amount of lycopene. H1311-DI supplemented mice consumed an average of 10.9 mg/kg bw/day of lycopene (for a 30 g mouse body weight), similar to what can be found in other rodent studies with lycopene supplementation (Zhu et al., 2020). Based on the benefits described from tomato lycopene supplementation in literature (Fenni et al., 2017; Luvizotto et al., 2013), we expected stronger metabolic health benefits for H1311 supplemented mice. Indeed, in our previous work, tomato powder supplementation or lycopene-rich beadlets alone displayed similar beneficial health effects in obesity-associated pathologies (Fenni et al., 2017), suggesting a specific role of lycopene. Nevertheless, this high lycopene tomato provided few to no observable health benefits on HFD-fed mice, among phenotypic traits associated to obesity improvement such as body weight gain, adiposity index, fasting blood glucose, glucose/insulin tolerance and liver lipids. Differences observed in the outcome of this study and previous works studying supplementation of tomato powder or lycopene in a diet-induced obesity may arise from lycopene bioavailability related to the post-harvest treatment and production of tomato powders. In this study, tomato powder was produced with cryogrinding and freeze-drying as to limit heat treatment and maximize tomato powder likelihood with fresh product. In industrial processes of tomato powder production, the initial

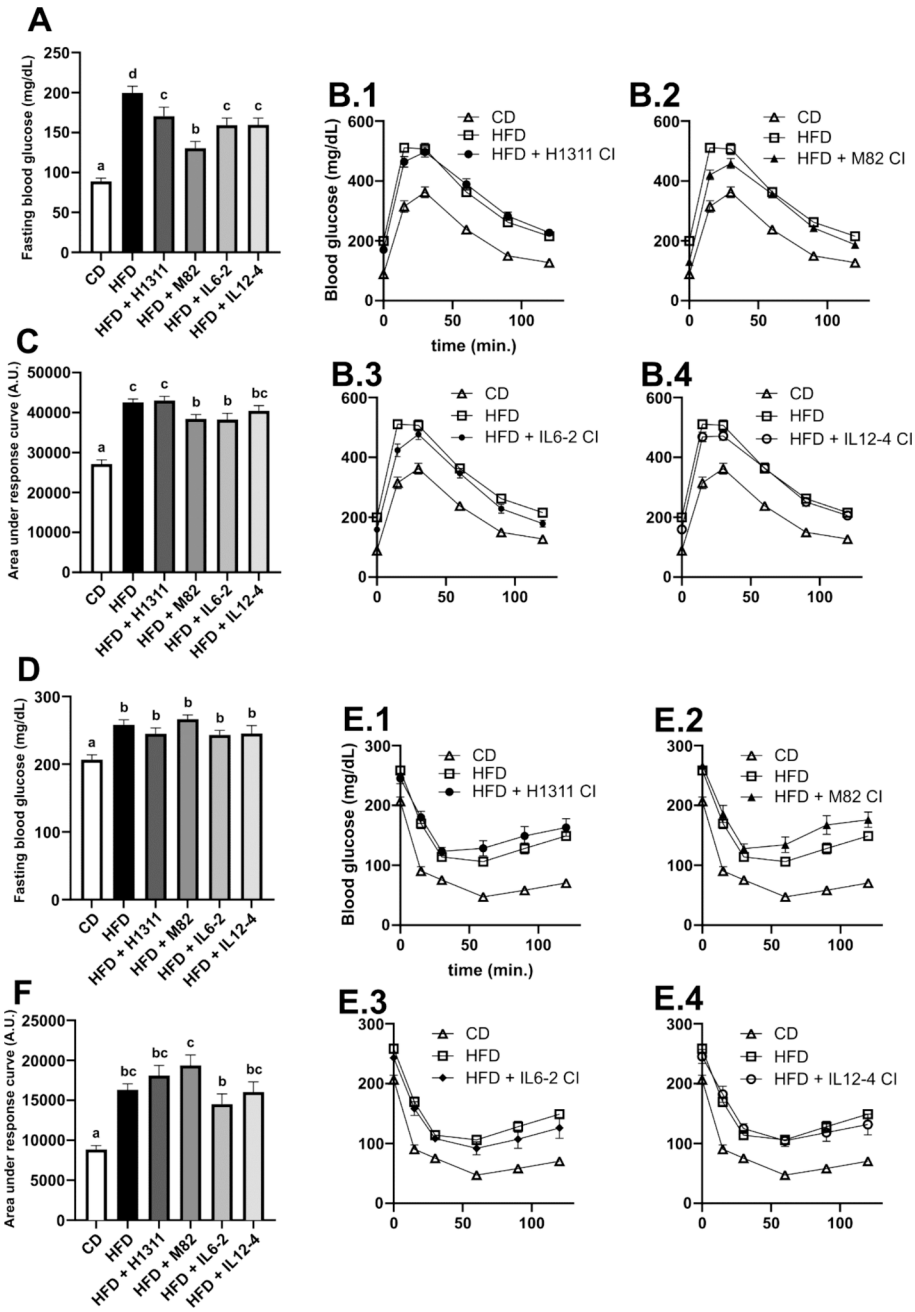

Fig. 4. Impact of tomato powder supplementation on glucose homeostasis. Overnight fasting blood glucose (A) and glucose levels during the oral glucose tolerance test (OGTT) (B1–B4) with the area under the glycemic response curve (AUC) (C). Six-hour fasting blood glucose (D) and glucose levels during the insulin tolerance test (ITT) (E1 – E4) with the AUC of the glycemic response curve (F). Values are presented as mean ± SEM (n = 10/group). CD = Control diet; HFD = High fat Diet. Letters indicate significant differences ($p < 0.05$) between groups, adjusted for multiple comparison with Benjamini Hochberg false discovery rate procedure.

Table 2
CD: control diet; HFD: high fat diet; HFD + […], high fat diet supplemented with a specific tomato genotype (H1311, M82, IL6-2, IL12-4) and irrigation regime (CI = Control Irrigation, DI = Deficit Irrigation). NEFA: non-esterified fatty acids. Values are presented as mean ± SD. Letters indicate significant differences ($p < 0.05$) between groups, adjusted for multiple comparison with Benjamini Hochberg false discovery rate procedure.

	CD	HFD	HFD + H1311-CI	HFD + H1311-DI	HFD + M82-CI	HFD + M82-DI	HFD + IL6-2 CI	HFD + IL12-4 CI
Triglyceride (g/L)	0.82 ± 0.14 a	0.86 ± 0.14 ab	1.03 ± 0.15b	0.87 ± 0.12 ab	0.98 ± 0.16 ab	0.87 ± 0.12 ab	0.89 ± 0.08 ab	0.83 ± 0.19 ab
NEFA (mmol/L)	1.18 ± 0.36 a	1.03 ± 0.22 a	0.86 ± 0.33 a	0.84 ± 0.27 a	0.92 ± 0.39 a	0.98 ± 0.41 a	1.07 ± 0.36 a	1.06 ± 0.35 a
Glycemia (mg/dL)	182 ± 21 a	233 ± 22c	226 ± 11 bc	238 ± 19c	241 ± 29c	216 ± 19 bc	202 ± 26 ab	228 ± 24c
Insulinemia (ng/mL)	0.07 ± 0.09 a	0.09 ± 0.07b	0.1 ± 0.06 ab	0.11 ± 0.09 ab	0.14 ± 0.09b	0.08 ± 0.09 ab	0.05 ± 0.06 a	0.1 ± 0.05 ab
HOMA-IR index	0.6 ± 0.82 a	3.38 ± 2.76c	2.74 ± 1.84 bc	2.99 ± 2.75 bc	3.03 ± 2.86 bc	2.5 ± 3.11 abc	1.13 ± 1.42 ab	2.49 ± 1.27 abc

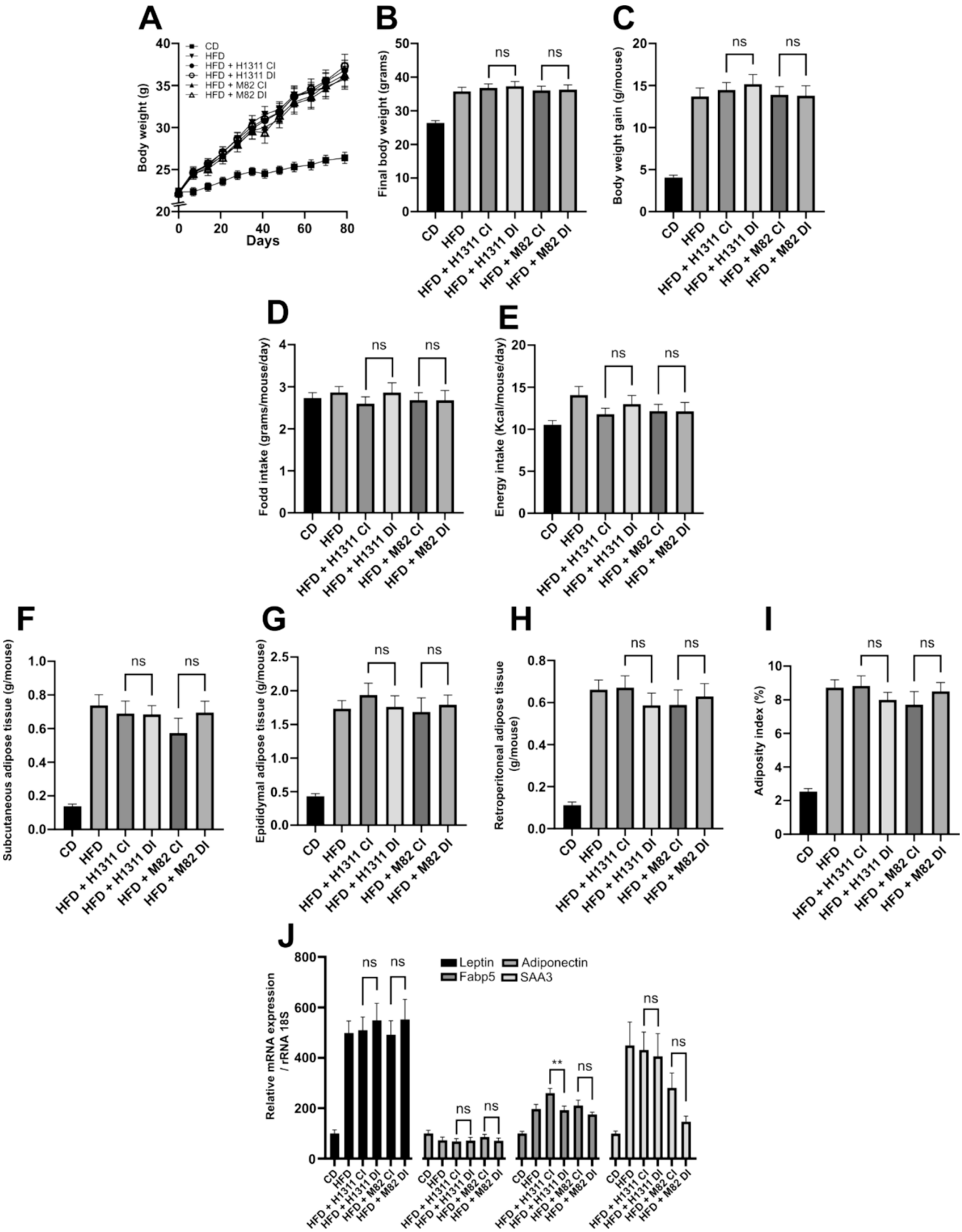

Fig. 5. Effect of tomato powder supplementation on morphological parameters, comparing control Irrigation (CI) and deficit irrigation (DI) production methods for H1311 and M82 genotypes. Evolution of animal body weight during 12 weeks tomato supplementation (A) with description of final body weight (B) and body weight gain (C) before animal sacrifice. Food intake as quantity (D) and energy (E) was established. After sacrifice, several adipose tissue deposits were weighted (F,G,H) to characterize adiposity (I). Values are presented as mean ± SEM (n = 10/group, except for D and E where n = 6/group). CD = Control diet; HFD = High fat Diet. Stars indicate significant differences between CI and DI supplemented animals within each tomato genotype (H1311 and M82) (ns: $p > 0.05$; *: $p < 0.05$; **: $p < 0.01$).

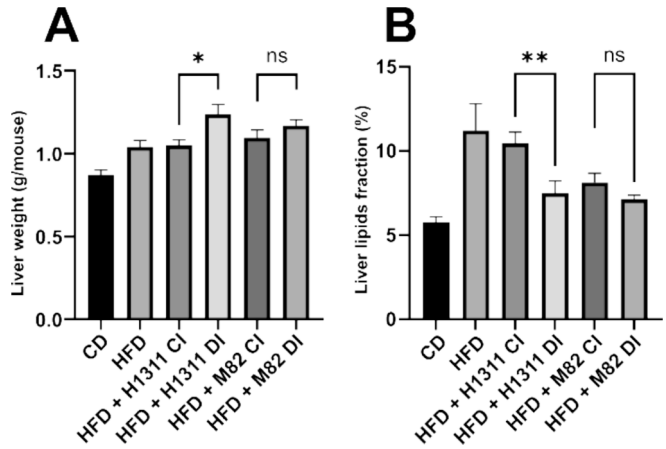

Fig. 6. Impact of control irrigation (CI) and deficit irrigation (DI) production methods for H1311 and M82 genotypes on mice liver weight (A) and liver lipids (B) after 12 weeks supplementation. Values are presented as mean ± SEM (n = 10/group). CD = Control diet; HFD = High fat Diet. Stars indicate significant differences between CI and DI supplemented animals within each tomato genotype (H1311 and M82) (ns: $p > 0.05$; *: $p < 0.05$; **: $p < 0.01$).

step consists to produce tomato concentrate via hot break or cold break process which strongly improve lycopene bioavailability in the final product (Page, Van Stratum, Degrou, & Renard, 2012). Then, the drying step is typically produced by spray drying or by tunnel dryer that implies moderate to high heat treatment to remove water from fruit (Qiu, Acharya, Jacobs, Boom, & Schutyser, 2019). Heat treatment and air exposure is generally associated with carotenoid oxidation and loss (Durigon, de Souza, Carciofi, & Laurindo, 2016; Qiu et al., 2019). In the meantime, heat could change lycopene isomerization and increase its cis/Z configuration, which is correlated to increased antioxidant capacity and bioavailability (Fenni et al., 2019; Toydemir et al., 2022). Overall, one could argue that different processing techniques used to produce tomato powder may change tomato powder health properties through different levers distributed all along the food processing chain (Toydemir et al., 2022). This last assumption will require further investigations.

It is noteworthy that IL6-2 powder differs significantly from the other tomatoes in terms of health effects. IL6-2-CI tomato supplemented group displayed improved health compared with the HFD group and compared with one or several other CI grown tomatoes for the following outcomes: Body weight gain (Fig. 2C), subcutaneaous adipose tissue (Fig. 2F), retriperitoneal adipose tissue (Fig. 2H), adiposity index (Fig. 2I), relative mRNA expression of leptin and Fabp5 (Fig. 2J), liver lipids fraction (Fig. 3B). Most outcomes taken together suggest this IL6-2-CI tomato mediates stronger beneficial metabolic effects than other tomatoes. The effects could be driven by the high β-carotene content supplied to IL6-2 supplemented mice (Table 1). Anti-obesogenic effect of β-carotene was previously suggested in both rodent and human studies (Amengual et al., 2011; Bonet, Canas, Ribot, & Palou, 2015; Coronel, Yu, Pilli, Kane, & Amengual, 2022; Landrier, Marcotorchino, & Tourniaire, 2012; Marcelino et al., 2020), possibly through the BCO1 (β-carotene 15,15′ oxygenase-1) mediated cleavage and conversion of β-carotene to retinoic acid. In mature adipocytes, retinoic acid may increase fatty acid oxidation, mitochondriogenesis and thermogenesis while inhibiting adipocyte differentiation (Coronel et al., 2022; Tourniaire et al., 2009, 2015). It is also for this tomato genotype that *FABP5* and *SAA3* gene expression were particularly downregulated compared to the HFD group, suggesting improvement in fatty acid transport and metabolism and decrease of inflammation status as previously suggested (Coronel et al., 2022; Karkeni et al., 2017). Several mechanisms such as the implication of retinoic acid on the activation of retinoid receptors or activation of transcription factors other than the canonical retinoid receptors have been described elsewere (Bonet et al., 2015).

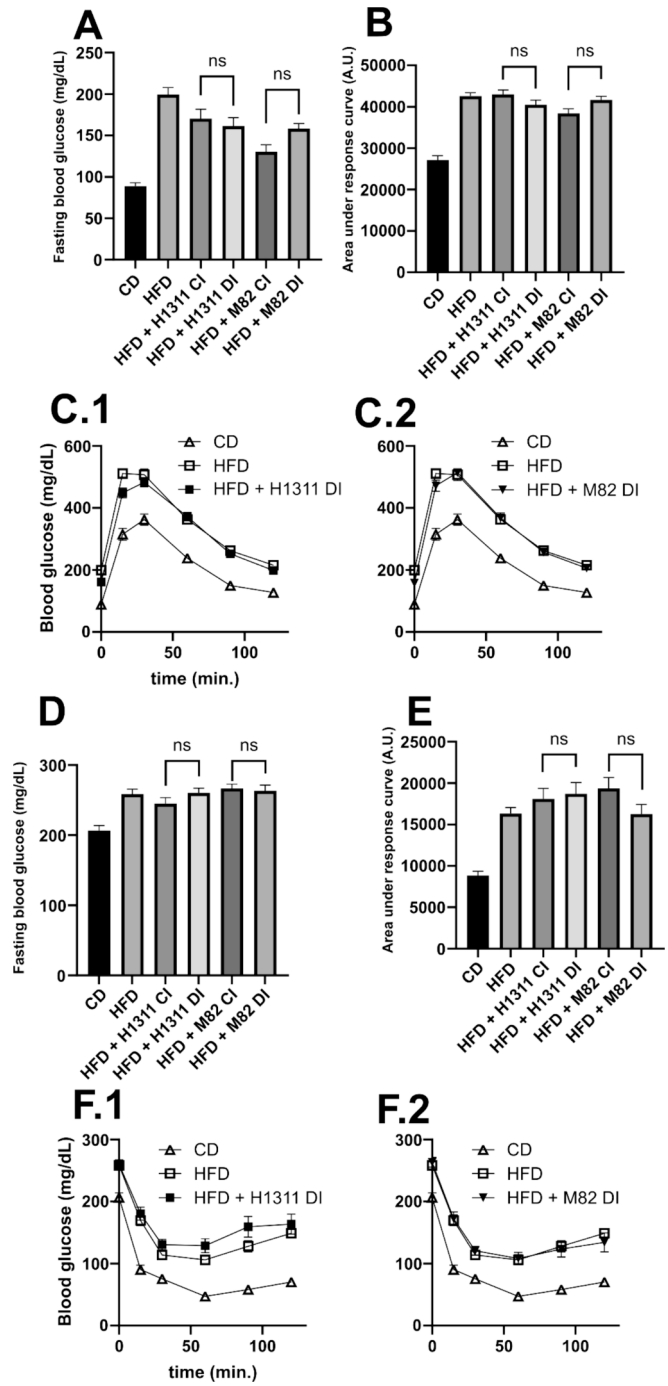

Fig. 7. Impact of tomato powder supplementation on glucose homeostasis, comparing control irrigation (CI) and deficit irrigation (DI) production methods for H1311 and M82 genotypes. Overnight fasting blood glucose (A), with the area under the glycemic response curve (AUC) (B), and glucose levels during the oral glucose tolerance test (OGTT) (C.1, C.2). Six hour fasting blood glucose (D) with the AUC of the glycemic response curve (E) and glucose levels during the insulin tolerance test (ITT) (F.1, F.2). Values are presented as mean ± SEM (n = 10/group). CD = Control diet; HFD = High fat Diet. Stars indicate significant differences between CI and DI supplemented animals within each tomato genotype (H1311 and M82) (ns: $p > 0.05$; *: $p < 0.05$; **: $p < 0.01$).

Two other tomato genotypes (M82-CI, IL12-4-CI) displayed beneficial effects on some parameters of animal metabolic health. Supplementation with M82-CI improved overnight fasting blood glucose, glucose tolerance and fatty liver compared to the HFD supplemented

animals. IL12-4-CI supplemented animals displayed improved overnight fasting glycemia and improved fatty liver compared to the HFD supplemented animals. Despite slight amplitude of the observed health effects, it remains of interest in terms of health since fasting glycemia is related to type 2 diabetes or prediabetes (Shin et al., 2013) whereas lipid accumulation in the liver is a hallmark of non-alcoholic fatty liver disease (Seebacher, Zeigerer, Kory, & Krahmer, 2020) which also represents a major challenge for public health. Such beneficial effect could be related to the anti-inflammatory effect of tomatoes, as recently reviewed (Landrier et al., 2023).

Overall, these results suggested that the tomato genotype had a significant consequence on metabolic health in obesity-induced mice model. Tomato genotype may considerably change the phytochemical cocktail in the fruit. It has been reported that cultivation method and genetics can have an impact on tomato carotenoids and other fruit compounds (Kuti & Konuru, 2005) and health effects of fruit consumption may result from a complex interaction among compounds, that remains poorly understood. While the tomato genotypes have been selected here for their contrast in carotenoid content, other phytochemicals beyond carotenoids included in the fruit matrix may participate in health properties. For example, chlorogenic acid was also present in doses ranging from 42.2 mg/kg for IL12-4-CI tomato powder to 153.6 mg/kg for M82-CI tomato powder. Chlorogenic acid has been identified as a putative candidate for body weight reduction and regulation of lipid metabolism (Cho et al., 2010; X. He et al., 2021). Similarly, among other carotenoids, lutein has been identified to improve metabolic health in diet induced mice obesity model (Gopal, Sukhdeo, Vallikannan, & Ponesakki, 2023), even if it is noteworthy that lutein contribution to total carotenoid content of tomato powders is limited (Table 2). The fact that IL6-2-CI, a β-carotene rich tomato, was associated to highly improved health status of animals compared with HFD animals, but presented a low chlorogenic or low total carotenoid content compared with other tomato genotypes (Table 1, Fig. 7), suggests that the high β-carotene content of IL6-2-CI may have a causal link to its health properties observed, probably through provitamin A mediated effects. Additional experiments are required to provide more details on mechanistic impacts of tomatoes on the most relevant health indicators, including glucose homeostasis.

In a global heating context, an increase of soil drought frequency and intensity can be expected, particularly for Mediterranean crops like tomatoes, resulting in lower yields (Cammarano et al., 2022). However, practices such as deficit irrigation could improve the overall quality of agricultural produce, which may compensate for the loss of yield. Data from literature suggested an increase of fruit carotenoids and/or other health related compounds under DI effect compared with fruits grown under CI condition (Hou et al., 2020; Lu et al., 2021; Martí et al., 2018; Ripoll et al., 2014). In this context, the two tomato genotypes tested under DI treatment (H1311-DI, M82-DI) were expected to improve metabolic health compared with their respective powders tested under CI (H1311-CI, M82-CI). Our results suggest that for each genotype, the phenotype of DI supplemented animals did not differ significantly from the CI supplemented animals (Figs. 5 and 7), except for the liver mass. The lack of discrepancy between CI and DI for a given genotype could be due to the relative low difference in terms of carotenoids content supplied to the mice (Table 1). H1311-DI supplemented mice displayed significantly increased liver mass, while the lipid content significantly decreased compared with H1311-CI supplemented mice (Fig. 6). Without reaching statistical significance, the same pattern of liver weight increases and liver lipid decrease was observed for M82-DI supplemented animals compared to M82-CI. Considering that this pattern is only discernible regarding the liver, it is hard to relate the underlying phenomena to other animal traits and tomato characteristics. The origin of such phenotype is presently not understood, the identification of the underlying mechanisms will require further investigation. Based on all animal health related results (Table 2, Figs. 5, 6, 7), CI and DI groups were compared for M82 and H1311 genotypes for a total of 23 outcomes. H1311-CI and H1311-DI groups differed significantly for 3 out of 23 outcomes (Fabp5 mRNA expression, Fig. 5J; liver weigh, Fig. 6A; liver lipids, Fig. 6B)). Similarly, M82-CI and M82-DI groups differed significantly for none of the 23 outcomes reported. In this case, it is worth noting that even if the DI did not improve metabolic health of animals, it did not mediate detrimental effects on measured parameters, suggesting that the nutritional quality of tomatoes was preserved, especially for the M82-DI supplemented animals that still displayed reduced fasting glycemia and liver lipid content.

5. Conclusion

The impact of 12 weeks tomato powder supplementation on metabolic phenotype on a male mice model of diet induced obesity revealed discrepancies on metabolic achievements between the different genotypes of tested tomato. The high total carotenoids/high lycopene content tomato powder improved the animal's phenotype to a limited extent compared to the animals supplemented with a low total carotenoids/high β-carotene content. In addition, our data suggested for the first time that a given genotype with deficit irrigation did not impulse a significant change on fruit health properties, but had reciprocally not major detrimental effect in terms of health effect compared with the control irrigation genotype. These experimental results highlighted the importance of tomato genotype and possibly tomato powder production process, which are too often overlooked in clinical or preclinical supplementation trials.

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CRediT authorship contribution statement

Thomas Breniere: . **Lorrine Bournot:** Investigation. **Flavie Sicard:** Methodology, Investigation. **Julien Astier:** . **Anne-Laure Fanciullino:** . **Catherine Riva:** Writing – review & editing, Supervision, Conceptualization. **Patrick Borel:** . **Nadia Bertin:** Writing – review & editing, Supervision, Resources, Project administration, Conceptualization. **Jean-François Landrier:** .

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.foodres.2024.114512.

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